CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN

A SINGLE ARM PROSPECTIVE STUDY

INSTITUTION

DEPARTMENT OF RADIOTHERAPY, BIRO
MADRAS MEDICAL COLLEGE

RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL

CHENNAI - 600003.

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY

EXAMINATION APRIL 2015

The Tamil Nadu Dr.M.G.R Medical University

Chennai - 600032.

CERTIFICATE

This is to certify that **Dr. A.RAMYA** has been a Post Graduate MD Student during the period from May 2012 to April 2015 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "**CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN**" is a bona fide work done by her during the study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

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ACKNOWLEDGEMENT

I thank **THE LORD ALMIGHTY**, for his eternal grace and guidance in helping me finish this study.

I express my sincere gratitude to **Prof.Dr.R.VIMALA, M.D.,** Dean, Madras Medical College, Chennai - 03, who has been a continuous source of encouragement. I am grateful to her for permitting me to conduct this study.

I express my sincere gratitude to **Prof. Dr.KALAISELVI, M.D**., Vice Principal, Madras Medical College, Chennai – 03 for her kind words of encouragement.

I express my gratitude to Chairman **Dr.C.RAJENDRAN M.D.**and the members of the Ethical Committee Council of Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai - 03, affiliated to The Tamil Nadu Dr. M. G. R Medical University, Chennai - 32 for having approved my study and for his valuable suggestions.

I express my gratitude to **Prof. Dr.M.VANITHA**, M.D., Director, Barnard Institute of Radiology and Oncology, Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai – 03, for her kind words of encouragement and inspiration.

I am extremely grateful to **Prof.Dr. S. SHANMUGAKUMAR, B. Sc., M.D, D.M.R.T.**, Professor & Head, Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 03 for bringing out an attitude of questioning everything and not accepting anything at face value. For his probing

questions to get to the basics of all subjects and making us think. I have benefitted immensely from his case discussions.

I am extremely thankful to **Prof.Dr.P.BALASUBRAMANIAM, M.D., D.M.R.T.**, Ex-Additional Professor, for his periodic monitoring, intellectual input, kind encouragement and support. Apart from his teaching, his systematic approach, his dedication, sincerity, the way he guides everyone are lessons I would like to inculcate for life.

I am gratified to **Prof.Dr.Kalaiyarasi,D.CH., M.D.,** Additional Professor **,** for her practical understanding of the subjects, the assignments she gave which helped me to improve my knowledge about the subject and she plays a major role in instituting the habit of daily reading. The feedback what she gives for the assignment and project paved way to explore many areas of the subject.

I am grateful to **Prof.,MUTHUVEL**., Professor & HOD, Department of Radiological Physics, for the support, encouragement and motivation rendered throughout the study period.

I wish to express my sincere gratitude to all the Assistant professors of our department (past and present) for guiding me during my study period. They guided me in acquiring the cases, planning the treatment, executing the chemotherapy and radiotherapy, manage the side effects during the treatment and much more.

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Dr.ARUN RAMANAN, M.D.R.T

Dr.PRABHAHARAN, DMRT

Dr.MADHARSHAH, D.M.R.T

I am indebted to the Medical Physicists of The Department of Radiological Physics who helped plan the radiotherapy and offered guidance during difficult situations,

Mr. THIRUMAVALAVAN Msc.,

Mrs. A. KOPPERUNDEVIMsc.,

My words of appreciation and gratitude also extends to our department radiographers **Mr. PURUSHOTAM, Mr. VIVEK** and their team of radiographers and students for their sincere execution of the treatment, kind support and service rendered for the patients in this study.

I am grateful to **Prof. DR. JAGDISH CHANDRA BOSE**, M.S., M.Ch, Professor and Head, Department of Surgical Oncology, and **PROF. DR. K. KALAICHELVI**,

M.D., D.M, Professor and Head, Department of Medical Oncology, for their prompt help rendered whenever approached.

My sincere gratitude goes out to my fellow post graduates and friends of our department for the magnanimous assistance offered to me throughout the study period.

I am also indebted to my husband **Dr.Jagadeesan** for his support and also to my family for their continuous support throughout my post-graduation.

Last but not least I wish to acknowledge the co-operation of my patients during the study period without whom this study would have been impossible.

DECLARATION

I solemnly declare that the dissertation titled "**CONCURRENT CHEMO RADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN**",a SINGLE ARM PROSPECTIVE STUDY was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during **March 2014 to August2014** under the guidance and supervision of Prof.Dr.S.SHANMUGAKUMAR.

The Dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University towards the partial fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy.

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CONTENTS

CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN

Dr.Ramya.A* Prof.Dr.S.Shanmugakumar; Prof.Dr.N.V.Kalaiyarasi;

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AIMS & OBJECTIVES:

To assess the immediate loco regional response rates and acute toxicity in patients with locally advanced squamous cell carcinomas of the head and neck in Conventional radiotherapy with weekly Cisplatin and Capecitabine.

MATERIALS AND METHODOLOGY:

Single arm prospective study with 30 consecutive patients with locally advanced head and neck cancer presented to the department of radiotherapy, Madras medical college, Chennai.

All patients were treated with conventional radiotherapy 66Gy along with weekly Inj.Cisplatin 40mg/m^2 and T.capecitabine 500mg/m^2 twice daily along with radiation.

The immediate loco regional response rates were assessed clinically and radiologically 6 weeks after concurrent chemo radiotherapy. The toxicity profile of the treatment was assessed with RTOG acute morbidity scoring criteria and CTCAE Version 4.

RESULTS:

Among 30 patients, Ca Oropharynx was 9 patients, followed by Ca Hypopharynx 8 patients, Ca Oral cavity with 7 patients and Ca Supraglottis 6 patients. 73% of patients had complete response and 27% had partial response. Toxicities observed in the study were Mucositis grade 3 in 5 patients and grade 4 in 2 patients; Skin reactions grade 2 in 2 patients. Leucopenia grade 2 in 2 patients. Systemic toxicity diarrhea grade 1 was only in 2 patients. There was no renal toxicity, hand foot syndrome in this study. There was no treatment related deaths in this study.

CONCLUSION:

Concurrent chemoradiotherapy with Inj.Cisplatin and T.Capecitabine in locally advanced squamous cell carcinoma of head and neck cancer is better regimen with manageable toxicity with higher complete response rate.

Key words: concurrent chemoradiotherapy, cisplatin, capecitabine, mucositis,hand foot syndrome

INTRODUCTION

Cancer is one of the most dreaded diseases in the world. In olden days the word cancer alone aroused fear in common people. In developed countries like the United States of America, it is one of the non-communicable notifiable diseases[1]. In India, incidence of cancer is rising; because of the increasing morbidity and mortality due to cancer, many states have made cancer notifiable and it is soon to become the first non-communicable disease notifiable to the center

Face is the index of the mind. Head and neck lodges the most crucial physiological functions like respiration, nutrition, language and expression most important unique feature of our mankind. Also it helps us to express our feelings from heart.

As the life expectancy of the population rises, there is an increasing incidence in the trend of cancer in the world. They pose a significant health problem especially in developing countries, including India. Due to high exposure to smokeless and smoke tobacco among Indian people, head and neck cancers in India continues to be a major public health problem and it causes significant morbidity and mortality.

Head and neck region cancers represent a heterogeneous group of cancers arising from the mucosa of upper aerodigestive organs, lined by

squamous epithelium. It comprises the cancers in the following anatomical regions, nasalcavity, nasopharynx, oral cavity, oropharynx, hypopharynx, the larynx, the salivary glands and the para nasal sinuses.

CANCER SCENARIO:

Every year around 5 million new cases of head and neck cancers are diagnosed worldwide[2]. Being sixth most common cancer in the world, it causes devastating effect on the individual by way of functional and cosmetic consequences. The head and neck cancer incidence has reduced in the developed countries with the awareness that smoking being the commonest cause and the subsequent decrease in smokers. Global burden rises to 14.1 million new cases and 8.2 million cancer deaths in 2012[2A].

In India, Squamous cell carcinoma of the head and neck is one of the commonest cancers in our country due to the widespread use of tobacco products in its various forms. Despite the steps taken by our government to create awareness with graphic warning labels on the tobacco products and a ban on the advertisements for tobacco products, Tobacco addiction has now become a common problem among youngsters resulting in the incidence of cancer at a very young age.

Head and neck cancers in India accounts for about 30% of all cancers in the males, constitute 11 to 16% in females. Over 200,000 cases

of head and neck cancers occur each year in India. Nearly 80,000 oral cancers are diagnosed every year in our country[3].

According to study published in Lancet in March 2012, the cancers related to tobacco represented around 42% of male and 18% of female cancer deaths in India. The most common fatal cancers in men are oral (including lip and pharynx) and lung.[53]

In Tamilnadu, MMTR states that most common cancer in men is head and neck cancer (19.23%) followed next by stomach cancer (13.98%) and lung cancer (12.46%). In women, breast cancer is the most common (20.87%) followed by cervical cancer (11.46%), stomach cancer (8.11%) and head and neck cancer (7.53%).

In our institute Barnard Institute of Radiology & Oncology, head and neck cancers constitute the majority of cases registered in our OPD. Majority of them are squamous cell carcinomas (~95%) with other histologies making up the remaining. Nearly 75% of them present in the locally advanced stage. Only around 20 to 25% of the cases present in the early stages. Most of them belong to poor socioeconomic status, tobacco users either in smoked form such as cigarettes, beedis or non-smoked forms such as pan etc.

ANATOMY:

The head and neck includes Oral cavity, Nasopharynx, Oropharynx, Hypopharynx, Larynx, para nasal sinuses, Nasal cavity, Salivary glands and Thyroid gland. This study includes patients only Oral cavity, Oropharynx, Hypopharynx and Larynx.

The Oral cavity includes Mucosal Lip, Buccal Mucosa, Alveolar Ridge, Retromolar Trigone, Floor of the Mouth, Hard Palate and Oral Tongue

Lip:

The lip begins at the junction of the vermilion border of the skin and includes only the vermilion surface. It is well defined into an upper and lower lip joined at the angle of mouth.

Buccal Mucosa:

Buccal mucosa includes the membranous lining of the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment of mucosa of the alveolar ridge (upper and lower) and pterygomandibularraphe.

Alveolar Ridge : Mucosa overlying the alveolar process of the mandible or maxilla and extends from the mucosal lining in the gingivobuccal sulcus; Lower alveolar ridge: extends to the line of free mucosa of the floor of the mouth. Posteriorly, to the ascending ramus of the mandible.

Upper alveolar ridge: from upper gingivobuccal sulcus to the junction of the hard palate, posteriorly to upper end of the pterygopalatine arch.

Retromolar Trigone: is the mucosal covering overlying the ascending ramus of the mandible from the last molar tooth to the apex superiorly, adjacent to the tuberosity of the maxilla.

Floor of the Mouth: Semilunar space overlying the mylohyoid and hyoglossus muscles extends up to the undersurface of the tongue. Its posterior boundary is formed by the base of the anterior pillar of the tonsil. The ostia of the submandibular and Sublingual salivary glands lie in the floor of mouth.

Hard Palate: Semilunar area between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones. It extends from the inner surface of the superior alveolar ridge to the posterioredge of the palatine bone.

Oral Tongue: The portion of the tongue which extends anteriorly from the line of circumvallate papillae to the undersurface of the tongue at the junction of the floor of the mouth. It is divided into the tip, the lateral borders, the dorsum, and the ventral surface of tongue.

PHARYNX: is divided into Nasopharynx, Oropharynx and Hypopharynx.

Oropharynx: this part of pharynx extends from the soft palate to the superior surface of the hyoid bone / vallecula. Oropharynx includes base of tongue, vallecula, soft palate, uvula, tonsil with anterior and posterior tonsillar pillar, glossotonsillar sulci and posterior pharyngeal walls.

Hypopharynx: Extends from the superior border of the hyoid bone to the lower border of the cricoid cartilage. It includes the pyriform sinuses (right and left), the lateral and posterior hypopharyngeal walls, and the post cricoid region.

The post cricoid area forms the anterior wall of the hypopharynx. It extends from the level of the arytenoids cartilages and to the plane of the inferior border of the cricoid cartilage.

The pyriform sinus extends from the pharyngoepiglottic fold to the cricopharynx and bounded laterally by the lateral pharyngeal wall, medially by aryepiglottic fold and the arytenoid and cricoid cartilages.

The posterior pharyngeal wall extends from the level of the superior surface of the hyoid bone to the inferior of the cricoid cartilage.

LARYNX: composed of several cartilages connected by ligaments and muscles. It is divided anatomically into the Supraglottic, Glottic, and Subglottic regions.

The Supraglottic larynx consists of the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids; the arytenoids are cartilages that articulate on the cricoid.

The glottis includes the true vocal cords and the anterior commissure.

The subglottis is 2 cm long and extends from 5 mm below the free edge of the true vocal cords to the upper margin of the first tracheal ring.

The preepiglottic space is bounded by the epiglottis posteriorly, the hyoepiglottic ligament and vallecula superiorly, and the thyroid cartilage and thyrohyoid membrane anteriorly and laterally.

RISK FACTORS:

The etiological factors of head and neck cancers point to the impact that lifestyle changes in past century had on our health. The principle risk factors are tobacco and alcohol.

TOBACCO:

According to National Cancer Institute reports 85% of patients with head and neck cancers have a history of tobacco usage. There exists a dominant and strong relationship between tobacco usage and squamous cell carcinoma of the head and neck (SCCHN).

1.SMOKING:

Development risk of SCCHN is directly correlated to duration and intensity of smoking[4].Smoking tobacco in the form of beedis, cigarettes, cigars, chutta/cheroot, dhumti, hookah and chillum is prevalent in India. Certain populations especially in coastal areas practice reverse smoking. About 50% men and 11% women between 15 – 49 years of age practice smoking in India[5,6]

Cigarettes are the main form of consumable tobacco worldwide. *Beedis* which consist of a small amount of tobacco flakes wrapped in temburni leaf with a colored string at one end are very famous in India.

The puff` rate per minute of a beedi is higher than that of an unfiltered cigarette which is responsible for the more carcinogenic load of beedis.

Nicotine is the major psycostimulant in tobacco. It increases the dopamine levels in nucleus accumbens and causes an incentive value and makes the habit to be repeated again and again causing addiction. The major carcinogens in tobacco causing cancer are PAH (polycyclic aromatic hydrocarbons), NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] and NNN(N1-nitroso nor nicotine).

SMOKELESS TOBACCO:

Globally there is a 60% increase in alternative nicotine delivery systems like snuff, lozenges. Betel quid is extensively used in India. It is also called as *pan* which consists of pieces of areca nut, tobacco and slaked lime. Added to this are spices, cardamom, cloves, according to the local preferences and are varyingly called as gutkha, zarda, mawa, khaini[9].

Oral sub mucous fibrosis is produced by chewing areca nut. Smokeless tobacco chewing is not an alternative to smoking tobacco. Indeed the content of nicotine and the carcinogens are manifold in smokeless tobacco[7,8].

ALCOHOL:

Alcohol has synergistic effect with tobacco. Duration, intensity and concentration of alcohol consumption directly correlates with oral cavity Cancer.[10,11]

A meta-analysis from 26 studies of oral and pharyngeal cancers found that consumption of 25, 50, or 100 g pure alcohol/day1 was associated with a pooled relative risk (RR) of 1.75, 2.85, and 6.01, respectively, of oral and pharyngeal cancer[13,14]Alcohol consumption also leads to immunosuppression, alcohol related diseases, altered behavior, unhealthy dietary pattern, and unstable emotional balance. All these factors have impact on cancer treatment and survival.

HUMAN PAPILLOMA VIRUS:

HPV infection is proved to be one of the causative factor in SCCHN.

HPV prevalence is about 30-35% observed in head and neck cancers, with

HPV-16 being detected in 60- 90% of infected cancer cases.[14,15] HPV prevalence has been found to be highest in oropharynx tumors(palatine tonsil),less common in the oral cavity[14-16].

The oncogenesis of SCCHN by HPV is by transformation of epithelial cells by viral oncoproteins E6 and E7 which inactivate the tumor suppressor genes p53 and pRbin the host cell leading on to increased cell proliferation and inhibition of apoptosis.[17-19]

HPV positive oropharyngeal cancers have characteristic features like

- Young patients,

- Nonsmokers

- Non alcoholics

- Present with locally advanced disease with large T and N stage

- Often with basaloid histology

- Poorly differentiated

-Sexually transmitted cancer due to oral sexual activity

-Better prognosis due to sensitivity to radiotherapy and chemotherapy has compared HPV negative SCCHN.

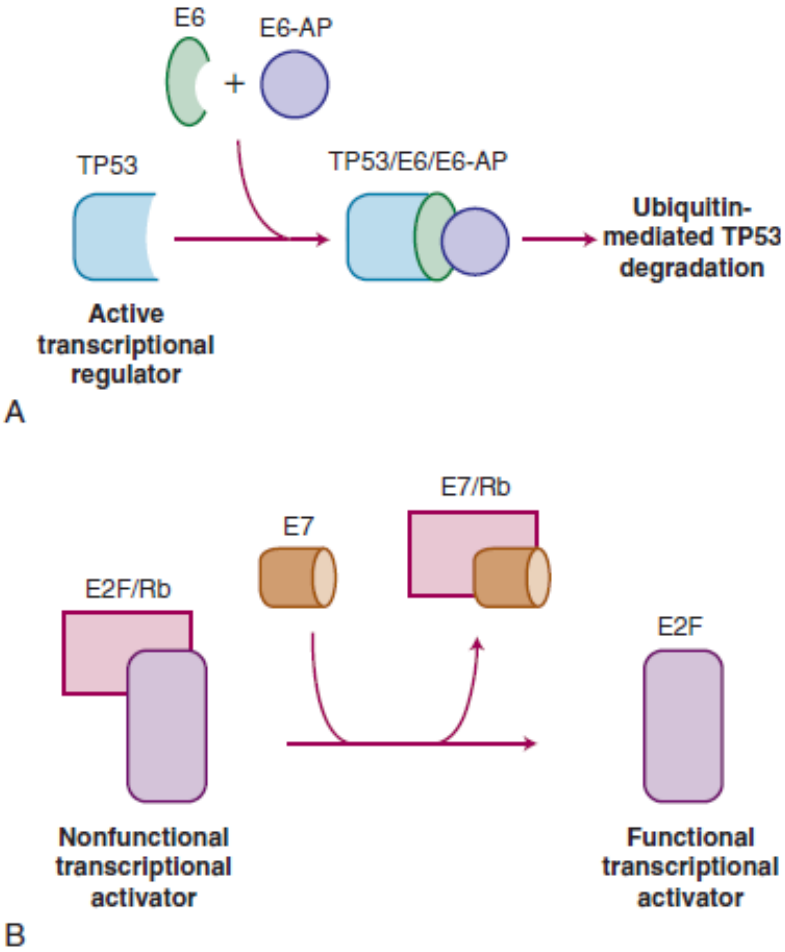


Figure no:1 HPV biological action

<u>OTHER RISK FACTORS</u>:

Diet deficient in antioxidants has been implicated to cause cancer in about 10% cases, spicy food consumption, sharp teeth, wood dust, heat fumes, sub mucus fibrosis etc

Plummer Vinson syndrome due to chronic iron deficiency and its association with post cricoid web can produce hypo pharyngeal SCCHN.

Chronic actinic exposure can produce cancer of lip.

PRECANCEROUS CONDITIONS:

Leukoplakia, Erythroplakia, Submucous fibrosis, Lichenplanus, Epidermolysisbullosa, Discoid lupus erythematosus etc[21].

Leukoplakia:

The most common premalignant lesion of the oral cavity. It is defined as a white mucosal patch or plaque,usually resolves with cessation of smoking.

Erythroplakia:

Reddish discolouration of the mucosa, 15-20% increased risk of cancer.

In a study done by Northern Ireland[22] states that, only 15% of dysplastic lesions and 1% of non-dysplastic lesions(epithelial hyperplasia, lupus etc) turn to neoplasia.

INHERITED CONDITIONS like Fanconi Anemia (FA), Ataxia Telangiectasia, Blooms Syndrome, & Li-Fraumeni Syndrome as increased risk of HNSCC.[23]

HISTOLOGICAL CLASSIFICATION:

Squamous cell carcinoma constitutes 90 - 95% of the head and neck cancers.

Remaining 5% are adenocarcinoma, verrucous carcinoma, minor salivary gland tumors, melanomas, adenoid cystic carcinoma, lympho-epitheliomas, and lymphoma, sarcoma, extra medullary plasmocytoma.

With respect to grades of differentiation based on keratinization, squamous cell carcinoma as three types;

Well differentiated : >75% keratinized

Moderately differentiated : 25-50% keratinized

Poorly differentiated: <25% keratinized.

The prognostic and predictive significance of histological differentiation is well established[24]

SYMPTOMS:

Most common presenting symptom is ulcer(or ulceroprolifertive lesion) followed by pain, difficulty in swallowing (dysphagia), pain during swallowing (odynophagia), difficulty in breathing (dyspnea), change in voice, and neck swelling because of lymph nodal involvement.

Other generalized symptoms are cough, weight loss, loss of appetite may cause further detoriation with treatment like concurrent chemoradiation. Nutritional status of the patient plays a major role in treatment outcome.

PROGNOSTIC FACTORS:

Unfortunately in India around 60% of head and neck cancers present in locally advanced stage (III & IV). In our institute 65- 70 % of total head and neck cancers are in the locally advanced stage. The reason may be due to poor socioeconomic status, lack of awareness and education, inaccessibility to treatment areas and fear of mutilating surgery[25]. Many psychosocial factors like beliefs like 'cancer a curse', 'ill-fated to have cancer', 'trivial ulcers in the mouth are self-limiting' and also the fear that the prolonged treatment will render the family stressful. Thus most of our patients present with advanced T stage with Lymph node involvement in which case single modality treatment is not possible.

Even with combined modality treatment local recurrences occur in 40-50% of the patients.

The following prognostic factors play a major role in locoregional control.[26]

TUMOR SIZE:

T stage major prognostic factor. Advanced T stage have poor prognosis.

NODAL INVOVLMENT: reduces the survival by 50%.

TUMOUR SITE: early Ca Larynx as good prognosis than oral cavity and hypopharynx.

Other factors like

Perineural invasion,

Postoperative positive or close margins,

Extra capsular nodal extension,

Depth of invasion.

MOLECULAR BIOMARKERS:

EGFR:

Studies show that 80- 95% of the squamous cell carcinomas of the head and neck are associated with over expression of EGFR receptors.[27,28]Activated, EGFR leads to cell proliferation, inhibits apoptosis, affects cell differentiation, increases cell motility, stimulates angiogenesis and is known to induce metastasis. This gives a therapeutic

target in manipulating receptor pathways in cancer cells with targeted agents, monoclonal antibodies, like cetuximab as shown benefit in the advanced stages.[29,31]

TYROSINE KINASES:

Downstream kinases responsible for various functional pathways – proven response with manipulating targeted agents like geftinib[35], erlotinib, dasatinib.[30]

P53 MUTATION:

Most common gene mutation observed in head and neck cancers. This p53 mutation is associated with worse prognosis because this gene is involved in cell cycle regulation and apoptosis. Poor response to chemoradiotherapy.

Other mutations include Cyclin D1, Bcl-2, STAT1 and 3, ERCC1.

HEAD AND NECK CANCER TREATMENT OVERVIEW:

Cancers of Head and neckhasa multimodality treatment which includes Surgery, Chemotherapy, Radiotherapy and upcoming targeted therapy. The main outcome should be locoregional control with function preservation.

SURGERY:

Emerging from the history of cancer treatment surgery plays a major role. Surgery has been the primary modality used in the treatment of head and neck cancers, since then. But surgery results in disfigurement and loss of function too. Though plastic surgery as developed in recent years with less morbid procedures, most of the patients do not opt for it.

The head and neck squamous cell carcinoma can be

Resectable, Unresectable or Inoperable

RESECTABLE:

The resection of advanced cancers of oral cavity, oropharynx, hypo pharynx or larynx is by an enbloc resection to attain negative surgical margins. An **adequate margin** of **1.5 cm to 2cm** is required to obtain a clear frozen section. Any suspected margin of < **2 cm** has to be examined by a frozen section.

A **clear margin** is defined as a distance of ≥ **5 mm** from the resected margin to the invasive tumor. A **close margin** is a distance of **<5mm**. Primary tumor is usually approached through a trans-oral, transcervical or, through mandibulectomy.

NECK DISSECTION:

The anatomy of neck node levels should be known before lymph node dissection. There are no capillary lymphatics in head and neck epithelium so tumor must penetrate lamina propria before lymphatic invasion to occur. Thus the involvement of lymph nodes in head and neck indicate that the tumor is locally advanced.

The lymph node levels of the neck are divided into seven levels.

Level I include Iasubmental nodes and Ib submandibular nodes.

Level II upper jugular nodes

Level III middle jugular nodes

Level IV lower jugular nodes.

Level V as posterior triangle lymphnodes.(spinal accessory chain lymph nodes)

Level VI pretracheal nodes, prelaryngeal and para tracheal nodes

Level VII mediastinal nodes.

Other regional nodes include

Suboccipital

Retropharyngeal

Parapharyngeal

Buccinator (facial)

Preauricular

Periparotid and intraparotid

Lymph node levels drain a particular site in head and neck. So surgery can be planned depending on this nodal region involvement.

Oral Cavity:

The primary site lip drains into Level I nodes with central part to submental nodes and angle of mouth to submandibular nodes. In case of oral cavity tumors mainly Level Ib submandibular and Level II nodes. Oral tongue as unique lymphatic drainage with Level Ib, II _IV; especially in lymphatics of tongue there is crossing over and thus bilateral nodal involvement is possible. Also tongue can have direct involvement of level IV node without Level Ib,II nodes involvement.

Oropharynx mainly drains to Level II and III involvement.

In case of Nasopharynx retropharyngeal lymph nodes are involved in 94% of cases or Level II in 90% of the patients. But it can involve Level II –V group of nodes.

In case of Hypopharynx bilaterality is common with involvement of Level II – IV group of nodes. Larynx – supraglottis drains to Level II – IV.

Other areas like paranasal sinses, middle ear, vocal cords have fewer or no lymphatics.

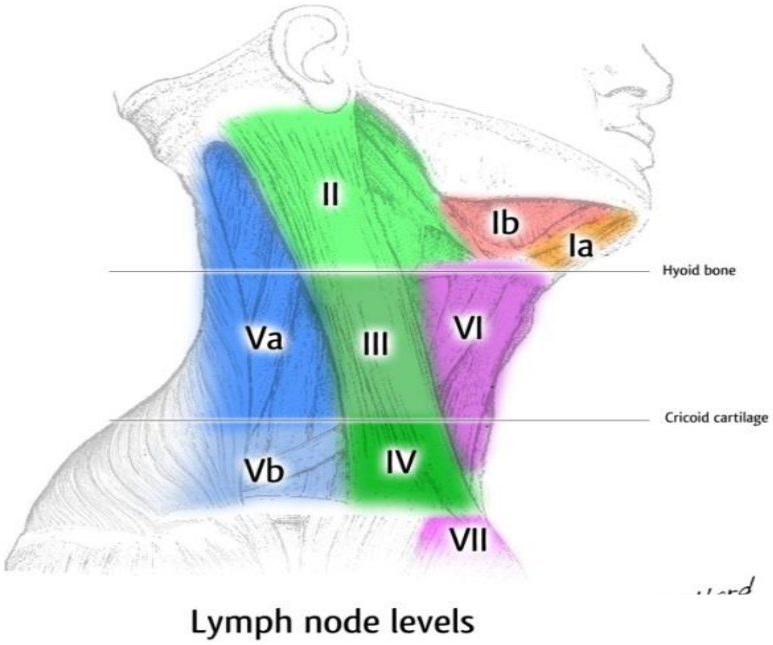


Figure no:2 neck node levels

In a **classic radical neck dissection**, the superficial and deep cervical fascia with its enclosed lymph nodes (levels I to V) is removed in continuity with the sternocleidomastoid muscle, the omohyoid muscle, the internal and external jugular veins, cranial nerve XI, and the submandibular gland. The radical neck dissection can be modified to spare certain structures with the intent of decreasing morbidity and improving functional outcome without compromising disease control[39].

There are three main types of **modified radical neck dissections**: type I—cranial nerve XI is spared; type II—cranial nerve XI and the internal jugular vein are spared; type III (functional)—cranial nerve XI,

the internal jugular vein, and the sternocleidomastoid muscle are spared. ***Selective*** **neck dissections** include the resection of lymph node levels that are at greatest risk for nodal metastatic spread. Types include the lateral, posterolateral, and supraomohyoid, which include resections of lymph node levels II–IV, II–V, and I-III, respectively.[32,33]

A modified or selective neck dissection is recommended for the cN0 neck, for selected clinically positive necks (mobile, 1–3 cm lymph nodes), and for removing residual disease after RT when there has been excellent regression of N2 or N3 disease.

UNRESECTABLE:

In a condition when adequate surgical clearance is not achievable, tumor spread to inaccessible areas like base of skull, infiltration into carotid artery, fixed nodes surgery is not an option.

INOPERABLE:

In such cases patient general condition is poor, metastatic disease such that surgery is not possible.

Patients completed chemo radiotherapy with residual disease may be amenable to **Salvage surgery.**

RADIOTHEAPY:

The concept of organ preservation as emerged ever since the Radiotherapy as proven its role in the treatment of cancer. Mainly in the Head and neck tumors it provides the major effect of organ preservation.

The discovery of X-Rays by William Roentgen in 1895. The first head and neck cancer to be cured by Fractionated Radiotherapy was in 1928 and since then various modalities and combinations with chemotherapy have been tried to increase the cure rate in these cancers.

Radiotherapy can be administered either Pre operatively, Post operatively or it can be definitive treatment with radiation alone in early stage tumors.

In case of postoperative Radiotherapy it should be administered after 4-6 weeks of surgery. Indications for postoperative radiotherapy are

- Advanced T stage,
- Multiple node positivity and
- Perineural or lymphovascular invasion.
- Post-operative chemo radiation is indicated in the case of positive margins and extra capsular extension.

The radiotherapy can be administrated in different types like

CONVENTIONAL FRACTIONATION:

As definitive modality dose of 66-70 Gy is recommended to the gross disease and 45 - 60 Gy to the subclinical disease. In a schedule of 2Gy per fraction 5 days a week.

ALTERED FRACTIONATION:

Accelerated Radiotherapy:

Decreases the overall treatment time so that the tumor cells regenerate less during the treatment and hence better loco regional control is achieved[36].

Pure accelerated radiotherapy:

There is a decrease in the overall treatment time but no change in the total dose or fraction size.

Hybrid accelerated fractionation: There are three types.

Type A: Drastic reduction in overall treatment time and a considerable decrease in the total dose.

Type B: Treatment time is decreased, total dose remains the same with an added break in between treatment(67.2 Gy in 42 fractions of 1.6 Gy twice daily over 6 weeks, including a 2-week break).

Type C(Accelerated concomitant boost): Total dose is same; overall treatment time is reduced with concomitant boostregimen (72 Gy in 42 fractions over 6 weeks, with 1.8 Gy daily for the first 3.6 weeks and 1.8 Gy [large field] plus 1.5 Gy [boost field], 6 hours apart, for the last 2.4 weeks)(36).

Hyper Fractionated Radiotherapy: Dose of radiation is increased, dose per fraction is significantly reduced, the numbers of fractions are increased and overalltreatment time is significantly unchanged(81.6 Gy in 68 fractions over 7 weeks, with 1.2 Gy given twice daily)

PALLIATIVE RADIOTHERAPY:

In patients who presents with very advanced stage, such cases cure is not possible as effort to alleviate the symptoms. Mostly given in Hypofractionated schedule.

CHEMOTHERPY:

Role of chemotherapy with radiation is proved in various trials[37,38]The MACHNC trial as proved overall survival benefit of 4% with addition of chemotherapy in a patient treated with surgery or radiotherapy.

Chemotherapy can be administered either as Induction, Concurrent or Adjuvant setting.

INDUCTION CHEMOTHERAPY:

It has proved that induction chemotherapy reduces distant metastases but no difference in overall survival.

The neoadjuvant setting as an organ preservation approach in laryngeal cancers-the Veterans Affairs trial[41] used chemotherapy in the neo adjuvant setting compared to concurrent chemoradiation to achieve organ preservation. . The use of induction chemotherapy using standard doses of cisplatin and 5 FU in various trials has shown a response rate of 60 to 90 % including 25 – 30 % complete response. It also decreased the incidence of distant metastasis probably because of the effect on micro metastasis in the circulation. But it failed to demonstrate any improvement in the survival. The recent phase III randomised trial DeCIDE trial which uses induction chemotherapy using docetaxel, cisplatin and 5FU followed by concurrent chemo radiation did not demonstrate any survival benefit from induction chemotherapy compared to concurrent chemo radiation.[42]

ADJUVANT CHEMOTHERAPY:

In case of postoperative setting with positive margins and extracapsular extension. Adjuvant chemo as a theoretical benefit of eradicating the sub clinical disease left behind after chemo radiation, also postulated that it sterilizes the micro metastasis present in the circulation and thereby prevent distal recurrence rate and improve overall survival rate. The increased sensitivity of minimal residual disease to anticancer drugs has been shown by cell cycle and growth fraction studies. Unfortunately these theoretical benefits are not proved by any randomised control trials and supportive evidence forthe routine use of adjuvant chemotherapy is far from definitive.

CONCURRENT CHEMORADIATION:

In the path of concurrent chemo radiation, initially trials was done with Bleomycin, Mitomycin, Cisplatin etc. But has the results of the Meta-analysis MACHNC [37] as clearly proved that Cisplatin as the drug of choice in concurrent chemo radiation. This trial has shown an absolute benefit of 6.5% $\pm$1% at the end of 5 years in overall survival with concurrent chemo radiation as compared to 2 % benefit with Induction Chemotherapy.

Thus Cisplatin is used in various trials in different regimens. Cisplatin in three weekly or weekly regimens can be used in any way the Cisplatin cumulative dose should be kept equal to or above 210mg (machnc-37).

PALLIATIVE CHEMOTHERAPY:

In head and neck cancers many different drug regimen as tried but no single agent has proven superior to others.

TARGETED THERAPY:

As already stated that EGFR receptors in over expressed in 85-90% of head and neck cancers. Inhibitors of EGFR like the monoclonal antibody Cetuximabhas used in many trials. The EXTREME trial[43] demonstrated that the addition of cetuximab to Cisplatin and 5 FU regimens in metastatic and recurrent head and neck cancer resulted in an improved overall survival. The landmark trial by Bonner et. Al[44] showed that addition of cetuximab concurrently to radiotherapy in locally advanced head and neck cancers resulted in a significant improvement in loco regional control and median OS.

The use downstream kinases inhibitors like geftinib and erlotinib have not shown any added benefit with its addition to the standard

therapies. Recently COX-2 inhibitors, farnesyl inhibitors, and proteasome inhibitors are under study for head and neck cancer.

PREVENTION OF HEAD AND NECK CANCER- upcoming concept:

As there is a concept of Field Cancerization which states that the entire upper aero digestive tract is subject to subcellular injury by exposure to carcinogens, hence susceptible to cancer formation. Thus a person with malignancy in upper aerodigestive is prone for 20% increased lifetime risk of second primary tumor. This may be due to genetic alterations in time. This forms the basis of chemoprevention.

Many trials with different chemopreventive agents has been tried. Mainly with Cis-Retinoic acid; RTOG (The Radiation Therapy Oncology Group) trial with 13-*cis*-retinoic acid in a multi-institutional setting, consisting 1400 patients with stage I or II cancer were accrued. Unfortunately, this trial was negative and did not show any benefit to low dose isotretinoin in the prevention of second primary cancers.Other chemo preventive agents being investigated are green tea extracts, curcumin extracts, soybeans etc.

Other methods of prevention will include:

1. Awareness regarding tobacco products. Regulations controlling the sale of tobacco products.
2. Awareness about sexual practices like oral sex resulting in HPV infection.
3. Abstinence from alcohol
4. Good oral hygiene
5. Good nutrient rich diet, fresh fruits and vegetables

RATIONALE OF THIS STUDY:

As the MACHNC trials clearly proved the benefit of adding chemotherapy concurrently with radiation shows improvement in overall survival of 8% at the end of 5yrs.Concurrent chemo radiation forms the treatment of choice in Locally Advanced Squamous cell carcinoma of Head and Neck (SCCHN)[37].

As the trials established Platinum based schedule gave best results, there is still ongoing search for better regimen with concurrent chemo radiation to improve immediate loco regional control and later overall survival.

Multiple single gents and various combination of drugs are being tested in trials all over the world.

Cisplatin (*Cis*-diamminedichloroplatinum):

Cisplatin reacts on two different sites on DNA to produce cross-links

like intrastrand (>90%) or interstrand (<5%).

Formation of DNA adducts results in inhibition of DNA synthesis, function and inhibition of transcription.

Binding to nuclear and cytoplasmic proteins may result in cytotoxic effects.

Cisplatin and 5FU:

Cisplatin and 5FU have been used in most trials of concurrent chemoradiation. 5-FU has adverse effects such as oral mucositis, diarrhoea which is exaggerated due to additive effect of radiation, and myelo suppression; these adverse effects can result in treatment-related hospitalization or mortality, thereby diminishing quality of life and reducing treatment compliance.

Cisplatin and Capecitabine:

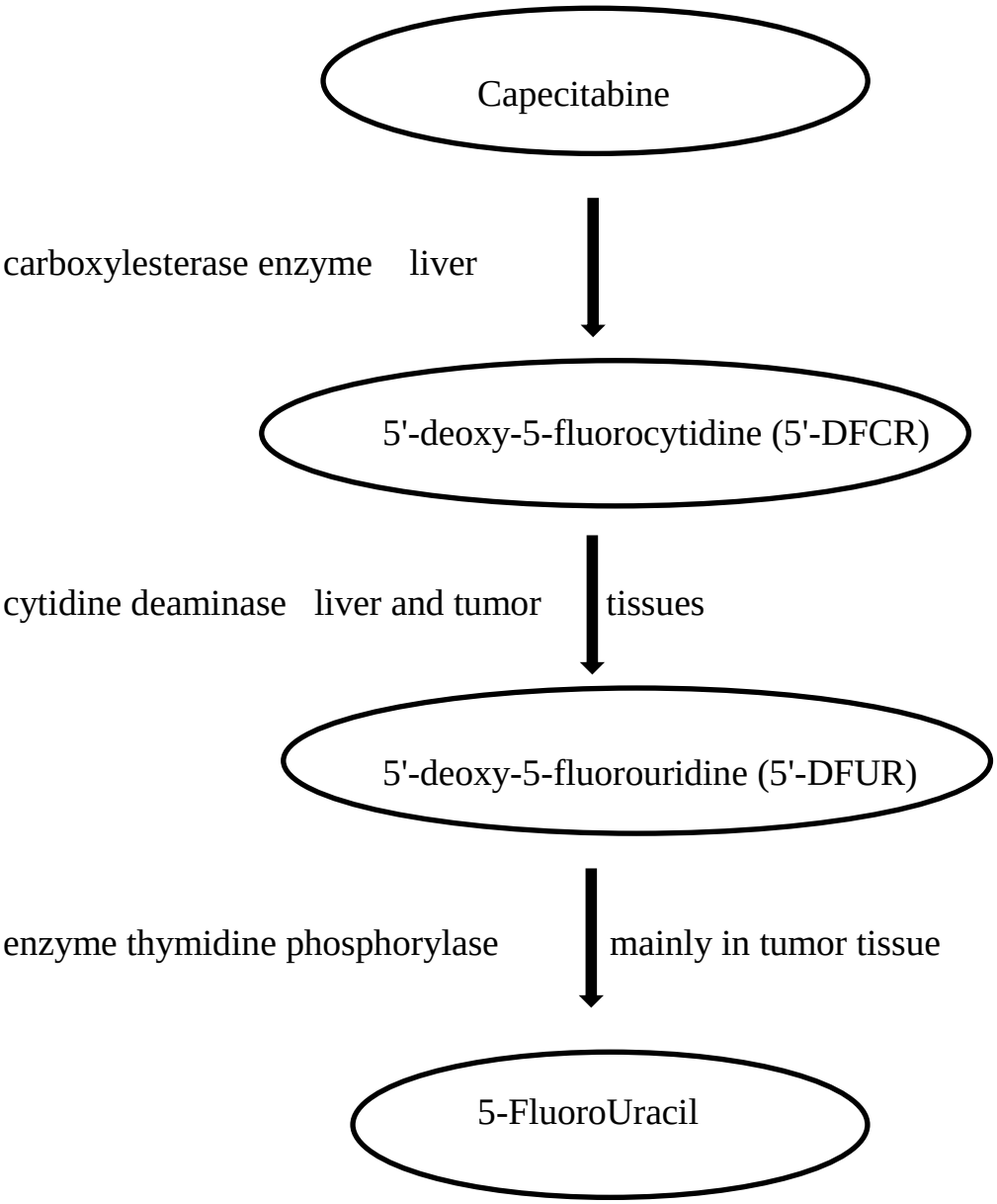
The oral fluoropyrimidine Capecitabine prodrug, itself is inactive; it was rationally designed to preferentially generate 5-FU in tumour tissue and mimic continuous infusion of 5 -FU. This selectivity is achieved through exploiting the significantly higher activity of thymidine phosphorylase (TP) in many tumour tissues compared with healthy tissue.[47]

METABOLISM OF CAPECITABINE:

Activation to cytotoxic forms involves 3 successive enzymatic steps.[46-48]

Metabolized mainly in liver by carboxylesterase enzyme into 5'-deoxy-5-fluorocytidine (5'-DFCR) and cytidine deaminase in liver and tumor tissues converts to 5'-deoxy-5-fluorouridine(5'-DFUR) finally the enzyme thymidine phosphorylase mainly in tumor tissue converts into 5-FluoroUracil

Metabolized mainly in liver



MECHANISM OF ACTION OF CAPECITABINE:

- The 5-FU metabolite FdUMP - Inhibits the target enzyme thymidylate synthase.

- 5-FU metabolite FUTP incorporates into RNA causing alterations in RNA processing and translation.

DNA INHIBITION:

- 5-FU metabolite FdUTPincorporates into DNA results in inhibition of DNA synthesis and function.
- Accumulation of dUMP due to inhibition of thymidine synthase causes subsequent misincorporation of dUTP into DNA, results in inhibition of DNA synthesis and function.

Capecitabine metabolism leads to 2.9-fold higher 5-FU concentrations in malignant compared with non-malignant tissues[49]. This results in a higher therapeutic index for Capecitabine compared with other fluoropyrimidines[50,51].

Rationale of dose reduction of Capecitabine:

Trials have shown that MTD (maximum tolerated dose) of Capecitabine concurrently with radiation was 500mg /m^2twice daily in locally advanced head and neck squamous cell carcinoma [52]. As a radiosensitizer Capecitabine increases the efficacy of radiation and cisplatin. Twice daily doses results in prolonged exposure of 5-FU. Also radiation up regulates the expression of the enzyme Thymidine Phosphorylase improves the efficacy of Capecitabine.

Since loco regional failure is the most common type of failure after therapy in locally advanced head and neck cancer, a regimen of concurrent chemoradiation with weekly cisplatin and Capecitabine daily has the potential to improve this without the systemic toxicity of full-dose chemotherapy.

CANCER TREND IN CHENNAI:

The trend of head and neck cancer from Madras metropolitan Cancer Registry clearly shows the rising incidence in a decade.

TREND OF HEAD AND NECK CANCER IN MMTR

Table no:1 Cancer trend

Head and Neck SITES				
PERIOD	MALE		FEMALE	
	CIR	ASR	CIR	ASR
1983-87	16.3	24.8	9.4	13.7
1988-92	19.0	30.0	9.9	14.7
1993-97	19.5	25.9	8.2	10.5
1998-02	20.7	25.0	8.7	10.3
2003-05	22.2	25.2	9.3	10.8
2006-08	22.9	25.2	9.3	10
2009-10	25.2	26.6	9.4	10.2

ASR: AGE STANDARDIZED RATE PER ONE LAKHS POPULATION.

CIR: CRUDE INCIDENCE RATE PER ONE LAKHS POPULATION.

Table no: 2, Head and neck cancer site (1)

Chennai Site	2003-05				2006-2008			
	CIR		ASR		CIR		ASR	
	Male	Female	Male	Female	Male	Female	Male	Female
Lip	0.3	0.1	0.3	0.2	0.2	0.2	0.2	0.2
Tongue	5.2	1.7	5.7	2.0	5.4	1.9	5.7	2.1
Mouth	5.1	4.2	5.7	4.9	6.6	4	7.1	4.5
Oropharynx	2.7	0.4	3.1	0.4	1.5	0.2	1.7	0.2
Nasopharynx	0.6	0.4	0.7	0.4	0.7	0.3	0.7	0.3
Hypopharynx	3.7	1.6	4.3	1.8	4.2	1.9	4.8	1.9
Pharynx Uns	0.5	0.2	0.5	0.2	0.6	0.3	0.7	0.3
Larynx	4.1	0.7	4.9	0.9	3.7	0.5	4.3	0.5
Total	**22.2**	**9.3**	**25.2**	**10.8**	**22.9**	**9.3**	**25.2**	**10**

Table no:3 Head and neck cancer site (2)

Chennai Site	2009-2010			
	CIR		ASR	
	Male	Female	Male	Female
Lip	0.4	0.4	0.2	0.2
Tongue	6.5	6.7	1.9	2.0
Mouth	7.4	7.6	4.4	4.8
Oropharynx	1.5	1.7	0.2	0.2
Nasopharynx	1.0	1	0.3	0.4
Hypopharynx	3.5	3.9	1.8	1.9
Pharynx Uns	0.6	0.6	0.2	0.2
Larynx	4.3	4.7	0.4	0.5
Total	25.2	26.6	9.4	10.2

LITERATURE REVIEW

LITERATURE REVIEW

As the history of cancer and its treatment emerged in concept from the late 19th century, newer techniques and combination of chemotherapy with radiation as proved its importance in loco regional control and progression free survival.

The use of Concurrent chemo radiotherapy depends upon the tumor radiobiology and physics. Surgery followed by postoperative radiotherapy was the standard approach in the case of locally advanced resectable head and neck cancers.

Conventional fractionation was considered as the best balance between tumor kill and normal tissue toxicity. It refers to a radiation dose of 2 Gy per fraction, five days a week, up to a total dose of 66-70 Gy[55]. This schedule was the first to be tried in the field of Radiotherapy and followed till date.

ALTERED FRACTIONATION IN RADIOTHERAPY:

EORTC trial by Horriet et al in 1992 - this trial compared conventional fractionation, 70Gy in 2Gy per fraction, 35-40# in 7-8 weeks, to hyperfractionation of total 80.5 Gy in 70 fractions in 7 weeks as 2 fractions of 1.15Gy per day. Patients included were T2-T3

oropharyngeal carcinoma, N0, N1 disease. In the final analysis it was found that the local control was significantly higher in case of hyperfractionation. Also at 5 years, 59% of patients had locoregional control in this arm compared to 40% in the conventional fractionation arm. This trial showed that the treatment regimen is an independent significant prognostic factor for loco regional control, which resulted in improved survival, without a significant difference in late toxicity.[56]

Another fractionation schedule using six fractions per week instead of five fractions showed improved tumor response. **DAHANCA 6 and 7** randomized controlled trial showed the benefit of short treatment time with six fractionation per week –due to the promising results of this trial, this schedule became the standard of management in Denmark. According to this trial the 5-year locoregional control rates were 70% vs 60% for the six fraction and five-fraction groups. The primary control was good but lymph nodes does not show any added benefit. This trial as increased acute toxicity but it was transient. [(57)]

RTOG 9003 trial compared hyperfractionation and two forms of accelerated fractionation to standard fractionation radiotherapy. The hyperfractionation arm delivered 1. 2 Gy/fraction bid for 5 days/week to 81.6 Gy/68 fractions/7 weeks; the accelerated fractionation included split

at 1.6 Gy/fraction bid, 5 days/week, to 67.2 Gy/42 fractions/6 weeks includes a 2-week rest after 38.4 Gy and another form of acceleration with concomitant boost at 1.8 Gy/fraction/day, 5 days/week and 1.5 Gy/fraction/day to a boost field as a second treatment daily for the last 12 treatment days to 72Gy/42 fractions/6 weeks. Hyperfractionation and accelerated fractionation with concomitant boost showed significantly better local-regional control than standard fractionation[36].

Although Hyperfractionation improves loco regional control, this occurs at the cost of increased acute toxicity which results in treatment breaks increased hospital stay.

Sequencing Chemotherapy with Radiation:

Chemotherapy provides benefit depending on the time of its addition with Radiation. The radiobiological basis of combining Chemotherapy with Radiation is to obtain maximum therapeutic benefit. Tumour cells have accelerated cell proliferation, hypoxia and acidity which are not present in normal cells. Similarly assessment of various mechanisms of resistance to radiation and different chemotherapeutic agents are also important to be considered.

Spatial cooperation: in this case radiation acts loco regionally and chemotherapy at a distant site, without any overlap.

Independent toxicity: the chemotherapy drugs given may have a different toxicity profile and it does not increase radiation reactions.

Enhancement of tumor response: in this case the ability of chemotherapy to enhance the radiation response is exploited. This resultin better tumor kill based on additive action. This however, does not include the cytotoxic action of the drug itself but only its radio sensitizing property, to prevent excess normal tissue toxicity.

If the overall cell killing in the combination treatment is contributed by individual cytotoxicity of the drug and individual effect of the radiation, then it is called **additive effect**.

If the cell killing in combined modality is greater than the cell killing by individual cytotoxic agents, then it is called as **supra additive effect.** This is possible when chemotherapeutic agents interact with radiation and potentiates the effect of later.

Inhibition of tumor repopulation: only in case of concomitant Chemoradiotherapy.

Protection of normal tissue: through administrationof agents which selectively prevent normal tissue damage

Improved tumor oxygenation: because of increased cell kill, leading to better local control.

There are numerous trials describing the time of Chemotherapy introduction with Radiation.

Induction chemotherapy:

The Department of **Veterans Affairs Laryngeal Cancer study Group** conducted a prospective randomised control study in locally advanced laryngeal cancer. The aim of this study was to compare the option of induction chemotherapy followed by radiotherapy with surgery reserved for residual or recurrent lesions is a feasible alternative to surgery followed by postoperative radiotherapy. Patients in the control arm received three cycles of induction chemotherapy using cisplatin and 5 fluorouracil. The patients were assessed after two cycles of chemotherapy. Any patient who failed to attain at least a partial response was taken up for immediate surgery followed by radiotherapy. Responding patients were allowed to complete three cycles of chemotherapy followed by definitive radiotherapy.[34]

The results of the trial showed that overall survival was same in both arms. The 3 year survival rate was 53%. The loco regional recurrences were greater in the control arm (12% vs 2%), but since salvage surgery was done in recurrent cases the overall survival was not compromised. Another interesting result is distant relapses were decreased in the chemo arm (11 % vs 17 %). But despite decrease in distant relapses overall

survival could not be improved. 64% of the patients recruited in the chemotherapy arm retained functional larynx.The authors concluded that in view of the high rate of local recurrences in the case of chemotherapy arm more effective local therapy is needed to achieve larynx preservation.

EORTC/TAX 323 (Vermorken et al. 2007) in this study 358 patients with stage III–IV head and neck cancer which was unresectable were randomized toTPF (docetaxel/cisplatin/5-FU) vs. PF (cisplatin/5-FU) induction chemotherapy followed by RT alone, delivered with conventional(66 Gy) or hyperfractionated (74 Gy) RT. Induction chemo with TPF increased median survival from14.5 to18.8 months, but increased hematologicaltoxicity and chemo-related death (2.3 vs. 5.5%). 10 -15% of patients after induction chemotherapy were unfit to receive Radiation in this study.[58]

Thus role of Induction chemotherapy followed by Radiation is acceptable only in selected patients prone for distant recurrences. This benefit can be achieved with the compensation of loco regional recurrence.

ADJUVANT CHEMOTHERAPY:

Adjuvant chemotherapy in Head and Neck following surgery is less studied.

Intergroup study 0034 used postoperative cases were randomized in into two arms. Study arm had 3 days of Cisplatin (100mg/m2), 21 day cycle and infusional 5 fluorouracil(1000mg/m2/day for 5 days, followed by radiation dose of 50-60 Gy Vs control arm had radiation alone without chemotherapy. There was no improvement locoregional control or overall survival but the incidence of distant metastasis decreased significantly from 30% to 20%.

RTOG 95–01trial with resectable tumors of the oral cavity, oropharynx, larynx, or hypopharynxincludes 459 patients who had 2 involved lymph nodes, nodal extracapsular extension, or positive margin randomized to postoperative RT (60–66Gy) vs postoperative chemoradiotherapy (60–66 Gy and cisplatin ×3cycles). This study was published by Cooper et al in 2004. The results were Chemo-RT improved 2-year Disease Free Survival (43→54%), Loco Regional Control improved from72% to 82%, and improved OverallSurvival (57→63%), but hadincreased grade 3–4 toxicity (34→77%).[59]

EORTC 22931published by Bernier et al in2004, this trial included

334 patients with resectablestage III/IV oral cavity, oropharynx, larynx, and hypopharynx cancer were randomized to postoperative radiotherapy (66 Gy) Vs postoperative chemoradiotherapy (66 Gy and cisplatin 100

mg/m2 on days 1, 22, 43). Allpatients received 54 Gy to the low-risk neck.Chemo-RT improved 3/5-year Disease Free Survival (41/36→59/47%), 3/5-year Overall Survival (49/40→65/53%), and 5-year Loco Regional Control (69→82%), but increased grade 3–4 toxicity (21→41%).[60,61]

Trials conducted by **EORTC** and **RTOG,** both showed post-operative chemo radiotherapy as improved Disease free survival and loco regional control but with increased grade 3&4 toxicity.

CONCURRENT CHEMORADIATION:

Concurrent chemoradiation in locally advanced head and neck cancer, the history tracks down to the era when Inj. Mitomycin, Inj.Bleomycin were used with Radiation. Initial trials done by NCOG, EORTC showed improvement in loco regional control and overall survival. Also there are trials with single agent Inj.methotrexate shows improve in loco regional control.

But with more understanding of the tumor radiobiology, radiosensitizers like 5- Fluorouracil and Cisplatin, either alone or together, have been tried in many studies and proved as effective & potent chemotherapy drugs to combine with radiation.

META-ANALYSIS OF CHEMOTHERAPY IN HEAD AND NECK CANCER (MACH-NC):

The first part of this landmark meta-analysis which was published in the year 2000by Pignon et al. This analysis included 63 randomized trials. The initial report from 1965-1993, showed a significant absolute overall survival benefit of 4%, both at 2 and 5 years ($p<0·0001$) in favour of chemotherapy.

Concomitant chemotherapy showed an absolute survival benefit at 2 and 5 years of 8%. In adjuvant setting, there wasn't significant effect of chemotherapy seen on survival, and similar was the case for neoadjuvant trials. There was, nevertheless, a significant benefit with platinum plus fluorouracil (hazard ratio 0·88, 95% CI 0·79–0·97). The effect of multiagent concomitant chemotherapy was significantly greater than single-agent chemotherapy (hazard ratio 0·69 vs 0·87,$p<0.01$). For the effect of chemotherapy on survival by covariate values, the only significant observation was a decreasing effect of chemotherapy on survival with increasing age (trend test, $p=0·05$).As far as timing of chemotherapy is concerned, there was a non-significant decrease in risk of death in the concomitant chemotherapy group. This meta-analysis included trials which were very heterogeneous and no solid conclusion

could be drawn regarding the routine use of chemotherapy and the regimen to be used.[38]

However, **the update** of this analysis, **published in 2009.** This included 93 randomized trials and demonstrated an overall absolute benefit of chemotherapy to be 6.5% at 5 years andthe hazard ratio was 0.81 ($p < 0.0001$). Whereas the absolute benefit of Induction Chemotherapy at 5yrs was 2.4% and that of Adjuvant Chemotherapy - 1.0$\pm$ 2.2 % .This absolute benefit in the meta analysis proves that Concomitant Chemotherapy as superior results and shows advantage over induction or adjuvant chemotherapy.

There wasn't significant difference in the benefit of chemotherapy on survival ($p=0.14$) between postoperative or curative radiotherapy with conventional or altered fractionation. Mono and poly-chemotherapy did not differ but the effect of chemotherapy was significantly higher ($p = 0.006$) with platinum than with other types of mono-chemotherapy agents. There was only one negative "cisplatin alone" trial in this meta-analysis which used a cumulative dose of 140 mg/m^2 suggesting that the total dose of Cisplatin should be considered. It was also demonstrated that there is a statistically significant decreasing effect of chemotherapy on survival with increasing age.[37]

This Meta-Analysis clearly states the benefit of concurrent Chemo radiotherapy in the squamous cell carcinoma of Head and Neck beyond any doubt.

Latest trial Concurrent Vs InductionChemo:

The DeCIDE, a phase III randomised trial using induction chemotherapy with Docetaxel, 5 fluorouracil and cisplatin in N2/N3 neck SCCHN(2012 ASCO meeting). Patients were randomised to chemo radiation alone with five days of docetaxel 25 mg/m^2, 5 fluorouracil 600 mg/m^2 and hydroxyl urea 500 mg bid concurrently with radiation 150 cGy bid or with two cycles ofinduction chemotherapy using docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5 fluorouracil 750 mg/m^2 for 5 days followed by the same chemo radiation. 280 patients were recruited to the study from 2004 to 2009 and the minimum follow up was two years. The primary end point was overall survival. From 142 patients randomized to induction, 91% received 2 cycles and 87% continued to chemoradiation. Grade 3-4 hematological toxicities were significantly higher in Induction Chemotherapy arm. The authors demonstrated that induction chemotherapy was associated with lower distant failure (DF) rates but an improvement in overall survival (OS) could not been validated. This was a negative study, as there was no overall survival difference with trends favoring the experimental arm in terms of disease-free survival.[62]

Another trial in ASCO 2012**PARADIGM trial**: with sequential chemoradiotherapy (induction chemo followed CCRT) versus concurrent chemoradiotherapy alone in locally advanced SCCHN : a randomised phase 3 trial-this study was conducted between 2004 to 2008, with a median follow up of 49 months 3-year overall survival was 73% in the induction therapy followed by chemoradiation group and 78%in the chemoradiation alone group (hazard ratio 1·09, p=0·77). Also, more patients had febrile neutropenia in the induction chemotherapy. Although survival results were shown to be good in both groups, there was no difference between those treated with induction chemotherapy followed by chemoradiation and those who received chemoradiation alone.

Both the DeCIDE and PARADIGM trial failed to show a significant survival benefit with induction chemotherapy, but the toxicity were high in the induction arm; The option of induction Chemotherapy followed by chemoradiation still can be considered in selected patients.

PLATINUM BASED CHEMORADIATION:

Concurrent chemoradiation with cisplatin as become the standard of care with the standard land mark trials. Cisplatin acts as a radiosensitizer increases efficacy of radiation even at low doses.

WEEKLY CISPLATIN Vs THREE WEEKLY CISPLATIN:

Due to the benefit and effectiveness of Inj.Cisplatin concurrently with radiation in Squamous cell carcinoma of the Head and neck , it is used widely in the dose of 100mg/m^2 day 1,22,43 regimen. This regimen as become the standard following many trials. But there are trials with smaller doses of Cisplatin which has proved to be quite effective. Though we are lack of the trials with direct comparison with low dose weekly Cisplatin and standard three weekly regimen; These nonstandard Cisplatin schedules have been preferred due to two main reasons – firstly, more frequent dosing may provide more radiosensitization during long course of radiation, and secondly, a smaller drug dose may have lesser chemotherapy related toxicity. With the three weekly regimen it was found that compliance to the schedule became a major issue, which is avoided in the case of smaller weekly doses. Based on trials like the Intergroup and RTOG – 0129, it has been suggested that the cumulative threshold dose of Cisplatin to achieve maximal benefit is 200 mg/m^2. Also, as discussed in the MACH-NC analysis, a dose below 140 mg/m^2 was found to have inferior results.

WEEKLY CISPLATIN TRIALS:

A study published from **TATA Memorial Hospital, Mumbai, by Tejpal Gupta in 2009**, compared high dose concurrent Cisplatin with

weekly Cisplatin 30 mg/m^2 with radiation dose of 70Gy. Planned was seven cycles of weekly Cisplatin, 65% of patients in the study received more than 85% of planned Cisplatin dose. With a mean follow-up of 19 months, the 5-year local control was 57%, loco-regional control was 46% and the disease free survival was 43% respectively.29% cases hadgrade 3 or higher acute mucositis and dermatitis in 35% cases respectively. This essentially manifested in patients receiving radiation dose ≥66 Gy and 6 or more cycles of chemotherapy.The conclusion drawn from the study was weekly cisplatin has moderate efficacy with acceptable toxicity. In country like ours where there are limited resources weekly cisplatin as the potential to become an optimal chemotherapeutic regimen[64].

Another study published by **Homma et al in 2011**, including 53 patients with locally advanced squamous cell carcinoma used weekly cisplatin 40 mg/m^2 on 7 weeks along with radiation of 70 Gy/2Gy per fraction in 35 fractions. The overall survival rate was 93.7% and disease free survival was 88%. The toxicity was manageable in all patients. The study demonstrated complete response rate of 98.1%.This study showed that weekly cisplatin is a feasible alternative with less toxicity without compromising the results. Major benefit is that the patients can be monitored frequently and dose adjustments can be made if required.[65]

Study published by **Ho and his colleagues in 2008** compared the differences in dose intensity, treatment delay, and toxicity between concurrent three weekly (80–100 mg/m^2) and weekly (40 mg/m^2) Cisplatin based chemo radiation in advanced head and neck. Most of the patients in weekly Cisplatin arm received a higher cumulative dose of 240 mg/m^2 or more as compared to the standard three weekly Cisplatin arm ($p = 0.04$). They also found that the three weekly regimen was associated with more delays (41% vs 29%) and omissions of chemotherapy (17.4% vs 5.6%) causing minimum number of patients to achieve a less cumulative cisplatin dose, potentially lowering dose-intensity.[66]

A similar study was conducted at the University of Florida, presented at the ASTRO 2009 meet, later published in Cancer J 2010. This study demonstrated that weekly Cisplatin 30 mg/m^2 decreases the treatment toxicity without sacrificing efficacy in patients treated with concomitant chemo-radiation for locally advanced head and neck squamous cell carcinoma. 79% patients in the study were able to complete at least 6 cycles of chemotherapy and 95% patients received RT up to at least 72 Gy. The 5-year actuarial outcomes in this study were as follows: Loco regional control rate of 79%; Distant metastases, 12%; and overall survival of 59%. It was claimed by the authors that the toxicity

rates of the study were lower than those reported for RTOG 9914 and 0129.[67]

The Basket University experience in weekly cisplatin concurrent with radiation was presented in conjunction with 2011 ASCO annual meeting presented by F Kose et al. A retrospective analysis of 53 eligible patients treated in the year 2007-2009 showed that there is no significant difference in median overall survival in weekly Cisplatin and three weekly cisplatin groups. The loco regional control and distant relapses were also similar in both groups. The conclusion of the study was concurrent chemo radiotherapy with weekly cisplatin is as effective as three weekly cisplatin with very high bolus dose.[68]

At University of Wisconsin, Tray nor et al studied the feasibility of weekly cisplatin with IMRT in locally advanced head and neck cancer. This study was conducted during a period of November 2001 to May 2007. A total of 57 patients were included and a weekly cisplatin dose of 30 mg/ m^2 was used. The prescription dose to the GTV was 70 Gy. The loco regional control was 85.5 % and median overall survival was 86.9%. The conclusion drawn from the study was weekly cisplatin 30 mg/m^2 along with IMRT with a GTV dose of 70 Gy is well tolerated.[69]

The landmark reviews and meta-analysis in the literature have not shown the inferiority of combination chemotherapy with radiotherapy in head and neck cancer. Trials have been done using Cisplatin with other agents like paclitaxel, in order explore more avenues for better outcome in head and neck cancer. Since 5-fluorouracil has proven to be the best combination drug with Cisplatin for the cancer of the head and neck by far in full dose regimens, this trial is conducted with Capecitabine Prodrug of 5-Fluorouracil,to prove its efficacy in locally advanced head and neck cancer.

TRIALS WITH CISPLATIN AND CAPECITABINE IN HEAD AND NECK CANCER:

Oral Capecitabine, prodrug of 5Fluorouracil, is used in solid tumors like oesophagus, stomach, pancreas, colorectum and its role in recurrent head and neck cancer is well established. The role in concurrent chemoradiation with Cisplatin/carboplatin is emerging in the 21st century.

Phase I study by **University of Virginia conducted by Christopher et al,** U.S.A to determine the maximum tolerated dose of Capecitabine given Concurrently with Carboplatin and Radiation. This study included eleven patients treated with Induction chemotherapy of carboplatin (AUC=2) in 6 weekly and Capecitabine up to 1,750 mg/m2

given orally or per gastric tube in divided doses on days 1-14 and 22-36. After a one-week break in the absence of progression, the patients received a second weekly chemotherapy 6 cycles and concomitant IMRT dose of 70Gy. The Capecitabine dose was studied in different schedule. This study proved the MTD for Capecitabine at 850 mg/m^2/day. Other grade 3 or 4 adverse effects, were due to the additive effects of radiation which did not meet DLT parameters: grade 3 mucositis and dysphagia (4 patients), local pain (3 patients), radiation dermatitis (2 patients), and fatigue (3 patients).The relatively low dose of Capecitabine given during IMRT, the rate of locoregional control in this study was excellent.

This trial concluded that the maximum tolerated dose of Capecitabine used Concurrently with Radiation is 850mg/m^2/day. The combination of Capecitabine and carboplatin has shown effective against HNSCC and the response rate was similar to that of Capecitabine and cisplatin.[70]

Another study by **Andrew J. Sykes et al, this is Phase 1 study** to establish the advantages of Capecitabine as a synchronous chemoradiotherapy agent in patients with Head and neck cancer. Capecitabine was given continuously throughout a week in bid dose starting at 350 mg/m2 bid. Radiotherapy dose was 55 Gy in 20 fractions

over 4 weeks. Capecitabine was given all days continuously with radiation without a break. A total of 24 patients were treated, out of which two patients developed DLT (grade IV mucositis) was reached at a Capecitabine dose of 550 mg/m^2 bid. So they reclined the dose to 500mg/m^2bid.Radiotherapy was completed without delay in all cases. Median follow up is 21 months. Complete clinical responses were seen in all cases. 2yr disease free survival is 83%.Four patients developed recurrence. This study concludes that Capecitabine can be given continuously with radiation without one week gap at a dose of 500mg/m^2 bid.[52]

Phase II study done by Jegannathen et al in 2011,to explore the efficacy of concurrent Oral Capecitabine with accelerated hypofractionated radical radiotherapy in locally advanced head and neck squamous cell carcinoma. 50 patients with stage III/IV SCCHN, of ECOG 0 to 2 were enrolled in this study during 2001-2004. The Capecitabine was given continuously at a dose was between 450 and 550mg/m^2 twice daily, for 28 days. The radiotherapy dose was 55Gy in 20 fractions/4 weeks, IMRT was not used. The complete response rate(CR), toxicity, locoregional control, overall survival(OS),disease-free survival(DFS) and cancer-specific survival was evaluated. The median age in this study was 55years; stage IV disease was 72%. After a median

follow-up of 6 years on the 30 surviving patients, 82% of patients completed the course of Capecitabine and 94% completed prescribed radiotherapy. Drug-related grade 3/4 acute toxicity (skin, bowel) was seen in 5 patients; grade 3 mucositis in 47patients. There weren't any treatment-related deaths, renal toxicity grade 3/4 haematological toxicity. At the end of 3 months CR was attained in 90% of patients. Relapse occurred in 34% of patients by 5 years. At 3yrs, locoregional control was 78%, overall survival 72%, cancer-specific survival 82% and DFS 62% and at 5 years were 72, 64, 75 and 56%, respectively. This schedule of synchronous Capecitabine for locally advanced SCCHN is well tolerated.[71]

As the immediate local control in this series as complete response was 90% and locoregional control at 3yrs and 5yrs was 78% and 72%, it was concluded that oral Capecitabine as a single agent targeted therapy given with each fraction of radiation as superior results comparable to other drug regimens like 3 weekly Cisplatin.

Study published by**Sherif A. Raafat et al done in Cairo University Egypt,** comparing the efficiency of concurrent Cisplatin versus oral Capecitabine with radical radiotherapy in locally advanced squamous cell carcinoma of the head and neck. Study was done during

2007-2009, 60 patients with stage III/IV head and neck cancer, ECOG 0 to 1 were enrolled in this study. 30 patients were given cisplatin 30mg/m^2 IV infusion weekly for 6 weeks with conventional radiotherapy. The remaining 30 cases were given oral capecitabine 500 mg/m^2bid, continuously for 28 - 35 days with conventional radiotherapy also. Radiotherapy dose was 66Gy in 2 Gy per fraction.73% of patients completed the entire course of Capecitabine and 80% completed prescribed Cisplatin. There were no treatment-related deaths or dose limiting toxicity. The complete response rate at 3 months was 77% in the Capecitabine group and 60% in the Cisplatin group. Relapse occurred in 10/30 (33%) patients after 2 years in the Capecitabine group and in 12/30 (40%) in the Cisplatin group. The median follow up period was 35 months for overall survival and 33 for disease free survival. The overall survival and disease-free survival rates at 2 years were 67%, and 85%, respectively for the Capecitabine group versus 60% and 73% for the Cisplatin group.

This study proved Synchronous chemoradiotherapy with Capecitabine was found to be very effective, with excellent response, local control and 3-year cancer-specific survival rates compared to the standard chemotherapy Cisplatin.

The complete response achieved with only Capecitabine as proved to be so effective that it can be given as a monotherapy in locally advanced head and neck squamous cell carcinoma.[72]

A study comparing the benefits of concurrent Capecitabine and Cisplatin versus concurrent cisplatin and 5-flurouracil in locally advanced SCCHN by **Seema Gupta et al, King George University Lucknow, 2013.** This study aimed to assess the efficacy and safety of both regimens in locally advanced squamous cell carcinoma of the head and neck. Out of 153 patients, with stage III or IV unresectable disease with no distant metastases and who had received two cycles of Taxol and cisplatin chemotherapy were randomly assigned to receive either concurrent cisplatin (75 mg/m^2 in day 1 and 2) or 5-FU (750mg/m^2 in D1-3) from the first day of radiotherapy at an interval of 21 days (Arm I) or cisplatin (75 mg/m^2 in day 1 and 2) and Capecitabine(750 mg/m^2 in two divided doses from day 1-14)from the first day of radiotherapy at an interval of 21 days (Arm II). The Radiotherapy dose was 66 -70Gy in 2Gy per fraction, 5 days in a week. If grade 3 or 4 Capecitabine/5-FU-related hematological or non-hematological toxicity such as mucositis, diarrhea, and hand-foot syndrome developed, Capecitabine/5-FU was discontinued until the toxicity resolves. Subsequently the Capecitabine doses was reduced by 20%, doses of 5-FU was reduced by 20-25%. The dose of

cisplatin was also reduced to 50% if the patient's creatinine clearance level was 30-50 mL/min. Cisplatin was withheld if the creatinine clearance level was less than 30 mL/min. If severe myelosuppression and febrile neutropenia develops CCRT was suspended for 1 week or interrupted. Results were Arm I, Complete response was 53.7% and Partial Response 41.8% while in Arm II Complete Response was 77.5% and Partial Response 16.9%. There were 56.7% primary and metastatic lymph node Complete Response and Partial Response 53.7% in Arm I while in Arm II there were primary and metastatic lymph node Complete Response 77.5% and Partial Response 78.9%. The quality of life among patients in this study, improved in Arm II because Cisplatin and Capecitabine as less complications and reduced hospital stay.[73]

These results showed that patients with Cisplatin and Capecitabine had a significantly better rate of complete response, fewer nodes, and better overall response compared to Cisplatin and 5FU patients. The two groups had a similar 3-year disease-free survival, progression free survival, and overall survival significantly. The quality of life also improved in patients with cisplatin and Capecitabine.

Study published in **British journal of cancer in 2005, by JG Kim et al,** to determine the efficacy and safety of concurrent

chemoradiotherapy with Capecitabine and cisplatin in patients with locally advanced SCCHN. This study enrolled 37 patients with unresectable locally advanced head and neck cancer. The chemotherapy schedule of two cycles of intravenous cisplatin of 80 mg/m^2 on day 1 and oral Capecitabine 825 mg/m^2bid from day 1- 14every 21 days. The radiotherapy dose was 70Gy in 2Gy per fraction, 5 days per week was delivered to the primary tumour site and neck. The primary tumour sites were oral cavity 6patients, oropharynx 11 patients, hypopharynx 8 patients, larynx 3, nasopharynx 6, and paranasal sinus 3. After the chemoradiotherapy, CR was attained in 78.4% and partial responses in 16.2% patients. Grade 3 or 4 neutropenia occurred only in two patients, grade 3 febrile neutropenia was observed only in one patient. After a median follow-up duration of one and half years, the estimated overall survival and progression-free survival rate at 2-year was 76.8 and 57.9%, respectively. Concurrent chemoradiotherapy with Capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced SCCHN provides very good complete response and overall survival.[74]

All these trials prove that Cisplatin and Capecitabine concurrently with radiation is a better regimen compared to Cisplatin and 5

Fluorouracil with increased complete response, locoregional control and overall survival with less toxicity.

Also there are trials that use Capecitabine, carboplatin with Taxol in the induction chemotherapy followed by concurrent chemoradiation with same in view of organ preservation in advanced, unresectable head and neck squamous cell carcinoma.

This trial was presented in **ASCO 2010, it is a phase II study published by D. F. Saragiotto et al** with patients who had biopsy proven stage III or IV SCC and no distant metastasis, PS 0 or 1, good organ function received two cycles of chemotherapy (CT) with i.v.Docetaxel 70 mg/m^2 on day 1 plus i.v. carboplatin AUC 5 on day 1 plus Capecitabine $1g/m^2$ orally daily bid every 28 days. Patients with disease progression or stable disease were excluded. Responding pts received two more cycles of the same CT concurrent with concomitant boost radiation therapy (72 Gy). The results 25patients enrolled in this study : 15 oropharynx, 8 larynx and 2 hypopharynx. All pts completed the Induction Chemotherapy and Concurrent radiotherapy. The response rate was 88% and only one patient had progression after 3 months of treatment completion. During Concurrent chemoradiotherapy, the rate of grade 3 febrile neutropenia was 36% and grade 3/4 mucositis was 72%. One

patient died during treatment as a result of a ruptured aortic aneurysm. 4.6 years of median follow up showed only one patient died as a result of metastatic disease.[75]

Three-drug induction therapy with Docetaxel, Carboplatin and Capecitabine 1g/m^2 followed by concurrent by the same agents and concomitant boost radiation therapy is feasible and very promising in a selected head and neck patient population, with high response and organ preservation rates.

The Capecitabine was also used in recurrent and metastatic squamous cell carcinoma in head and neck after platinum based treatment. A study by Martinez et al, this study included patients with recurrent head and neck after concurrent chemoradiation with platinum based regimen. This study included 40 patients all patients had Capecitabine 1250mg/m^2 bid,D1-14, every 21 days; all patients received four cycles. Overall response rate was 24.2%. PFS and OS were 4.8 and 7.3 months, respectively. Hematological toxicitygrade3/4 were reported in six patients. Other toxicity were palmar-plantar erythroplasia(10%), mucositis (10%), dysphagia (10%) and diarrhoea (7.5%).[79]

This study proved the efficacy of Capecitabine in recurrent head and neck squamous cell carcinoma. But Capecitabine is used mostly in curative concurrent chemoradiation in most of the trials.

Although all the land mark trials show Cisplatin and 5 fluorouracil has the standard combination with radiation; the toxicity with 5FU such as mucositis, diarrhea which is increased along with radiation causes increased hospitalization and treat breaks. Capecitabine prodrug of 5-FU as equal efficacy and reduces the toxicity produced by 5-FU. Also Capecitabine is a oral drug increases patient compliance to the treatment.

The reason for combining cisplatin and capecitabine with radiation in this present study are mainly because of the mechanism of interaction of the two drugs.

Mechanism of interaction: Cellular hypoxia, cell cycle age distribution, intrinsic radio sensitivity of the tumour are important factors that determine the sensitivity of the tumour to radiation.

HYPOXIA:

Radiation kills the cancer cells by generating reactive hydroxyl free radical with the cellular water. In the presence of oxygen, the reactive free radical will react with the DNA strand, resulting in permanent DNA

damage. Oxygen will supply electron to the damaged DNA strand and destabilize the strand break. This enhancement effect of oxygen in radiation therapy is known as oxygen enhancement ratio. Without the electron supply from oxygen under hypoxic condition, the DNA damages induced by radiation could be repaired by the cancer cells. Chronic hypoxia will lead to amplification of certain oncogenes like ras, c- myc, c-raf-1 which are responsible for increased resistance to radiation. Also the radiation generates oxygen free radicals which damages DNA. It is also postulated that due to hypoxia chemotherapy drug diffusion distance is increased. This causes decreased amount of chemotherapy drug to enter the actively dividing tumor cells.[76]

Thus by combining radiation with a chemotherapeutic drug which is active against hypoxic cells, we can overcome this resistance to radiation. Cisplatin is active against hypoxic cells. In Capecitabine metabolism, the main key enzyme Thymidine phosphorylase expression is increased in hypoxic conditions.

Cisplatin alkylates the DNA and causesintrastrand and interstrand breaks, thereby makes it more vulnerable to radiation. It not only increases the damage caused by radiation but also inhibit repair of the radiation damage. Cisplatin inhibits the repair of sub lethal damage(SLD)

and potentially lethal damage (PLD). It also causes inhibition of cell repopulation and modification of the slope of dose response curve.

The sensitivity to radiation varies widely depending upon which phase of the cell cycle, the cell lies. The G2 and M phase are three times more sensitive to radiation than S phase. The most radio resistant phase is S phase followed by early G1 phase. The exact mechanism for this is not known. This mechanism is exploited therapeutically in concurrent chemo radiation strategies. Most of the chemotherapeutic agents kill proliferating cells which are situated in the well oxygenated area. These areas lies close to capillaries hence they are easily accessible to chemotherapeutic agents. When these proliferative cells are killed, the bulk of the tumour is decreased and the interstitial pressure falls. This result in opening of closed capillaries and previously hypoxic cells become oxygenated. Since the tumour shrinks, the previously hypoxic areas move nearer to capillaries. Finally the loss of oxygenated cells results in more availability of oxygen to previously hypoxic cells which become oxygenated and susceptible to radiation. Tumour cells have accelerated cell proliferation, hypoxia and acidity which are not present in normal cells. Also the expression of the enzyme thymidine phosphorylase is increased in conditions with hypoxia, poor perfusion

and acidosis. This is the condition in most of the solid tumours mainly head and neck cancer.

Due to the preferential activation the enzyme thymidine phosphorylase, Capecitabine concentration inside the tumour cell is higher compared to the normal tissues. Also the concentration of Capecitabine is higher than that of infusional 5FU, Capecitabine treatment leads to 2.9 times higher concentration of 5 FU in the tumour cell compared to non-malignant tissues.[45, 50]

Thus concurrent chemoradiation with Cisplatin and Capecitabine is a better regimen compared to Cisplatin and 5 Fluorouracil. Also has previously described weekly Cisplatin is preferred than three weekly cisplatin because of less toxicity, patient compliance to the treatment without breaks. If the cumulative dose of weekly cisplatin reaches > 200mg/m^2, it has same efficacy compared the three weekly dose 100mg/m^2. Also with trials described Capecitabine can be used continuously with radiation in low dose of 500mg/m^2 twice daily.

This regimen of weekly cisplatin and daily Capecitabine has been tried in squamous cell carcinoma cervix also, shown better results.[77]

Based on above studies the present study was formulated and done in our department.

AIM & OBJECTIVES

AIM & OBJECTIVES

The aim of this study was to evaluate the use of Capecitabine and weekly Cisplatin concurrently with conventional radiation in locally advanced squamous cell carcinoma of head and neck.

Primary Objective:

To assess the immediate loco regional response rates in locally advanced squamous cell carcinomas of the head and neck treated with Capecitabine and weekly cisplatin concurrently with conventional radiation.

Secondary Objective:

To assess the acute toxicity to the treatment concurrent chemoradiation with Capecitabine and weekly cisplatin.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

STUDY DESIGN:

This was a Single arm prospective study with a Phase II design.

STUDY DURATION: March, 2014– August, 2014

STUDY CENTRE:

Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical college, Chennai.

SAMPLE SIZE:

30 consecutive patients with histopathologically proven squamous cell carcinoma of head and neck who fulfilled the inclusion criteria were recruited in the study from the outpatient department.

The intent of treatment was to be radical, aiming for cure, considering their disease stage, co- morbidities and performance status.

ETHICAL COMMITTEE APPROVAL: Approval from the institute ethical committee was obtained on 11.03.2014.

INFORMED PATIENT CONSENT:

All patients enrolled in the study were informed about the merits and demerits of participating in this study and signed an informed consent form in their regional language, which is Tamil.

INCLUSION CRITERIA:

- Biopsy proven newly diagnosed squamous cell carcinoma of the head & neck.
- Primary tumor sites: oral cavity, oropharynx, hypopharynx, larynx.
- Age 20 - 70 years.
- Stage III or IV, non-metastatic locally advanced head and neck squamous cell carcinoma.
- ECOG 0-2.
- No major life threatening comorbidities.

EXCLUSION CRITERIA:

- Patient who did not consent for chemoradiation at any point of time during treatment.
- Patients with history of any malignancy previously and received treatment for the same.
- Recurrent tumors.
- Tumors of nasal cavity, paranasal sinuses and nasopharynx.

- Non Squamous Histopathology
- Abnormal hepatic function, renal function, bone marrow reserve.
- Patients with uncontrolled co morbid conditions like diabetes, hypertension.
- Pregnant females.

PRE TREATMENT WORK UP:

1. Detailed history elucidation.

2. Complete physical examination by inspection, palpation.

3. Upper aerodigestive tract evaluation by direct and indirect laryngoscopy, anterior and posterior rhinoscopy and endoscopy if indicated to know the extent of disease and rule out a second primary.

4. Biopsy from the primary tumor or fine needle aspiration cytology from the metastatic lymph node.

5. Blood grouping and typing.

6. Complete blood count.

7. Renal function test.

8. Liver function test.

9. CT scan of the head and neck, plain and contrast, before initiating treatment and also after treatment for response assessment.

10. Chest X ray postero-anterior view.

11. Cardiac evaluation and fitness.

12. Naso-gastric tube insertion if indicated

13. Dental prohylaxis including scaling, dental filling and extraction if required.

14. Tumour stage, performance status and weight were recorded.

Staging was done based on American Joint Committee staging manual 7th edition (for head and neck cancers).

15. Weekly CBC, RFT, LFT before each cycle of chemotherapy.

PATIENT PREPARATION DURING TREATMENT:

All patients enrolled in the study were distributed pamphlets describing in brief the do's and don'ts while on treatment and later.

Quitting alcohol and tobacco

The harmful effects of tobacco, both in smoking and nonsmoking form, and alcohol were explained to the patient and draw backs of its addictions to treatment was explained. These addictions has inferior outcome after treatment and has increased risk of second malignancy due to field cancerization effect.

Dental health:

Chemoradiotherapy to oral cavity poses an increased risk of dental caries. As the production of saliva is altered both in quality and quantity

by concurrent chemoradiotherapy which leads to alteration of normal flora. Thus causes increased risk of caries formation due to mucositis and dryness. Oral discomfort due to mucositis can lead to decrease in brushing and flossing, also increases the risk of dental caries, which may lead to extraction, soft tissue necrosis, bone exposure, and osteoradionecrosis.

Dental care

Prior to irradiation all patients underwent dental evaluation; scaling and filling. Non-salvageable teeth were extracted prior to radiotherapy to reduce the risk of osteoradionecrosis. A gap of two weeks was given after dental prophylaxis for proper healing of gums. Prophylactic antibiotic treatment was started following extractions if necessary.

Edentulous patients were evaluated for their oral hygiene any retained root tips.

Patients were advised not to wear dentures until the mucosa is healed from the effects of radiotherapy.

Patients were advised to use soft brush and fluoride containing toothpaste daily during and after radiotherapy.

Mucositis

The major side effect of chemoradiotherapy is mucositis, a condition where patient perceives pain due to inflammation and ulceration of the mucosa. It occurs mainly due to disruption of normal mucosal barrier by chemoradiotherapy causes production of Reactive Oxygen Species resulting in increased production proinflammatory cytokines (IL-1β, IL-6) which causes tissue injury and apoptosis of cells in the mucosa.

Retrospective review of over 200 head and neck cancer patients treated with radiotherapy at MD Anderson cancer centre, 66% of the patients had either grade 3 or 4 mucositis. According to various studies patients with oral cavity, nasopharynx, oropharynx cancer treated with concurrent chemotherapy or altered fractionation radiotherapy, had a higher rate of mucositis producing intense pain, weight loss, and treatment breaks which compromises loco regional control.

Studies shown that daily dose, cumulative dose and volume of irradiated tissue determine the severity of mucositis. This pain produced by mucositis can lead to nutrition compromise thereby lack of proper hydration and oral hygiene. The desquamated epithelium, fibrin, and

polymorphonuclear leukocytes in a moist background provide a favorable environment for opportunistic infections such as candidiasis.

Thus in this study patient were suggested following oral measures to improve their oral hygiene during radiation.

- Patients oral health were monitored daily during treatment.
- All patients were advised to gargle 20 to 25 mL of indigenously prepared mouthwash by dissolving three teaspoons of soda bicarbonate and three teaspoons of table salt (sodium chloride) in 200ml of distilled water, for every 4 to 6 hours.
- Morphine sulfate mouthwash was used as an alternative to produce pain relief .Alcohol free commercial mouth wash was also used.
- Patients who developed mucositis were managed in addition with antibiotics and low dose corticosteroids. Oral candidiasis was treated with tablet Fluconazole 150 mg per oral for 7 days.

Other precaution:

Patients advised to restrain coarse and hot food items as they serve as irritant and exacerbate mucositis.

Oral physiotherapy - in the form of mouth stretching and mouth opening exercise also advised to patients to avoid trismus.

NUTRITIONAL CARE:

Most of the Head and neck cancer patients suffer from dysphagia and odynophagia either because of the tumor or due to treatment related effects like mucositis. This can affect the quality of life results in decreased food intake and they become nutritionally deprived resulting in weight loss.

All patients enrolled in this study were given dietary advice and encouraged to take easily available, nutritionally rich local foods, dairy products and fresh fruits and juices (avoid citrus fruits, acidic and spicy foods). Everyone encouraged to take supplemental calories before treatment daily two eggs and milk.

Homemade preparation of health mix which is rich in protein, was suggested to regenerate tissue protein. Small soft meals, in the form of bland diet at room temperature was advised. Protein supplements were given to patients. All patients were monitored for weight loss every week and special meals were designed for individual patients.

Mostly during third or fourth week of radiation patients develop severe mucositis. and need supplementary nutrition. Parenteral nutrition was also given if needed.Those patients who developed grade 3 or 4

dysphagia were treated with a naso-gastric tube insertion so that nutrition was not compromised.

Before initiation of treatment, it was made sure that all patients had normal blood, renal and liver function tests and everyone had given written consent for the treatment.

TREATMENT PROTOCOL:

30 locally advanced head and neck cancer patients were selected consecutively from the outpatient department, who then underwent the pre treatment work up as mentioned before. Following that they were treated with concurrent chemoradiation with Capecitabine and weekly Cisplatin and radiotherapy in a conventional fractionated manner.

RADIATION THERAPY:

All patients were treated with a conventional dose schedule of 2 Gy per fraction with a Theratron Phoenix Tele Cobalt-60 machine.

Patient Position:

Patients were made to lie in the supine position with neck slightly extended.

Patient Immobilization:

Strict immobilization was practiced while irradiating the patient.

Radiation Portals:

Patients were treated with opposing lateral radiation portals.

Verification:

X-ray simulation was done with the patient in treatment position to verify the treatment field.

Radiation Dose:

Patients were treated with a dose of 2 Gy per fraction, with 5 fractions per week, up to a total dose of 66Gy. Aim was to complete radiation within 6.5 weeks. Appropriate shielding was done to limit the spinal cord dose to 40 Gy as per the institutional policy.

Dose constraints:

Following were considered:

- Tolerance dose of spinal cord- 45 Gy in conventional fractionation for 5 to 10 cm.

-Parotid - up to 26 Gy after which permanent xerostomia is expected to occur.

CHEMOTHERAPY SCHEDULE:

Inj**.**Cisplatin 40mg/m^2 diluted in 500 ml normal saline,infused over 2 hours, every week on Mondays, during radiationto a total of 6 - 7 cycles

in 6.5 weeks..Tab.Capecitabine 500mg/m^2 twice daily, combination of 500mg,150mg tablets throughout the period of irradiation. Intake of Capecitabine is not consistent with the timing of radiation. Renal and hematologic parameters were assessed prior to each cycle of chemotherapy.

PREMEDICATION:

All patients were pre hydrated with one pint of normal saline over one hour before starting chemotherapy.

Premedication given 30 minutes prior to chemotherapy included the following:

- Inj. Ondansetron 8 mg IV.
- Inj. Dexamethasone 8mg IV.
- Inj. Ranitidine 50 mg IV.
- Inj. Chlorpheniramine 4mg IV.

Injection Cisplatin 40mg/m^2 mixed in 500 ml of normal saline and infused at 40 drops per minute in about 2 hours. Following this 500ml of normal saline was infused again over an hour.

Blood investigations were repeated every week before chemotherapy and hemoglobin < 10g% was corrected by blood transfusion. Colony stimulating factor was given when the Absolute

Neutrophil Count fell below 1000 cells/cubic millimeter. Symptomatic thrombocytopenia was corrected by platelet transfusion.

ASSESSMENT DURING CHEMORADIATION:

Toxicity Assessment:

Patients were reviewed every day before radiation for any acute toxic reactions and infections. Reactions like skin desquamation, mucositis, laryngitis, dysphagia etc. were recorded and graded based on RTOG acute radiation morbidity criteria. If a patient developed grade 3 or higher reactions chemoradiation was suspended. Careful attention was given for maintenance of hydration, adequate dietary intake and good oral hygiene.

Hematological and renal parameters were assessed on a weekly basis before every weekly dose of chemotherapy. As already described hematological parameters were assessed and treated. If renal parameters are raised adequate hydration was done and nephrologist opinion obtained.

RESPONSE EVALUATION:

All patients were reassessed by clinical examination and with a CT Neck, 6 weeks after completion of concurrent chemo radiation.

Response to treatment was described based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria.

- **COMPLETE RESPONSE**: Disappearance of all target lesions; malignant nodes <10 mm.
- **PARTIAL RESPONSE:** At least 30% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study; confirmed at 4 weeks.
- **STABLE DISEASE**: Neither partial response nor progressive disease criteria are met, in a minimum time set by the protocol.
- **PROGRESSIVE DISEASE:** At least 20% increase in the sum of the diameter, with a minimum absolute increase of 5 mm, taking as reference the smallest sum in the study or appearance of new lesions.

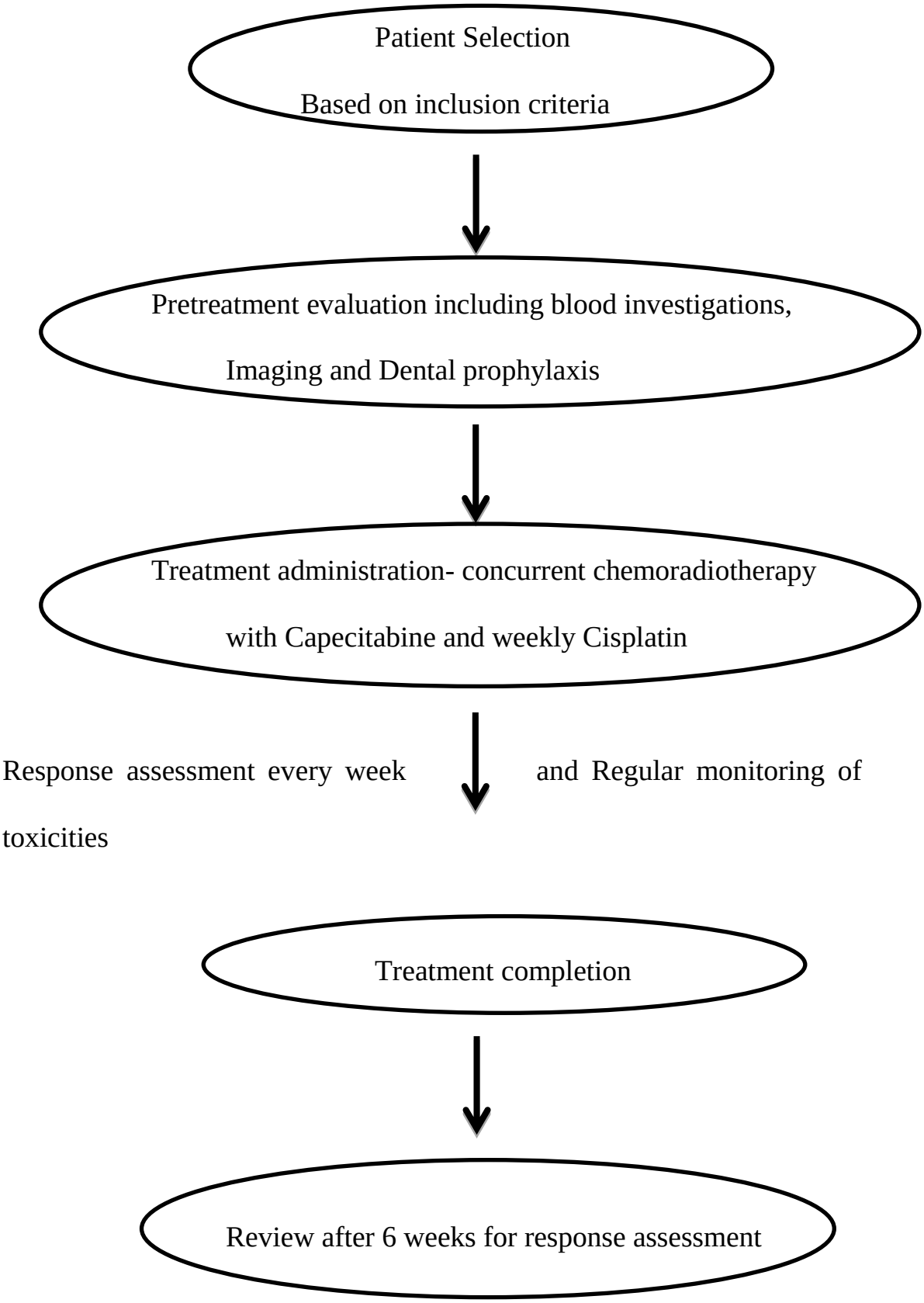
FOLLOW UP:

- Patients after completion of concurrent chemoradiation were discharged from the hospital. Response evaluation was done based on RECIST criteria after 6 weeks.
- Chest imaging, dental evaluations were done when indicated clinically. Continued smoking cessation, counseling to the patient and attender, rehabilitation, speech and swallowing therapy.

STATISTICAL ANALYSIS:

The patient factors, tumor factors, response to treatment, and toxicities were thoroughly analyzed. The results are expressed in percentage. Since this study is single armed one and also the sample size was only 30, the levels of significance cannot be commented on.

TREATMENT PROTOCOL



RESULTS

AND

ANALYSIS

RESULTS AND ANALYSIS

The total 30 patients recruited completed their entire treatment protocol and all of them were available for analysis of results.

PATIENT CHARACTERISTICS:

AGE DISTRIBUTION:

43% of the patients belonged to the age group 51- 60yrs, followed by 41 -50yrs. The mean age of presentation was 55.5yrs. The youngest patient age was 35yrs and the oldest was 64yrs.(figure no:3)

Table no: 4, AGE DISTRIBUTION OF THE STUDY POPULATION

AGE GROUP	NUMBER	PERCENTAGE
31- 40yrs	6	20%
41 -50yrs	9	30%
51-60yrs	13	43%
61-70yrs	2	7%

Figure no:3,Age distribution of the study population

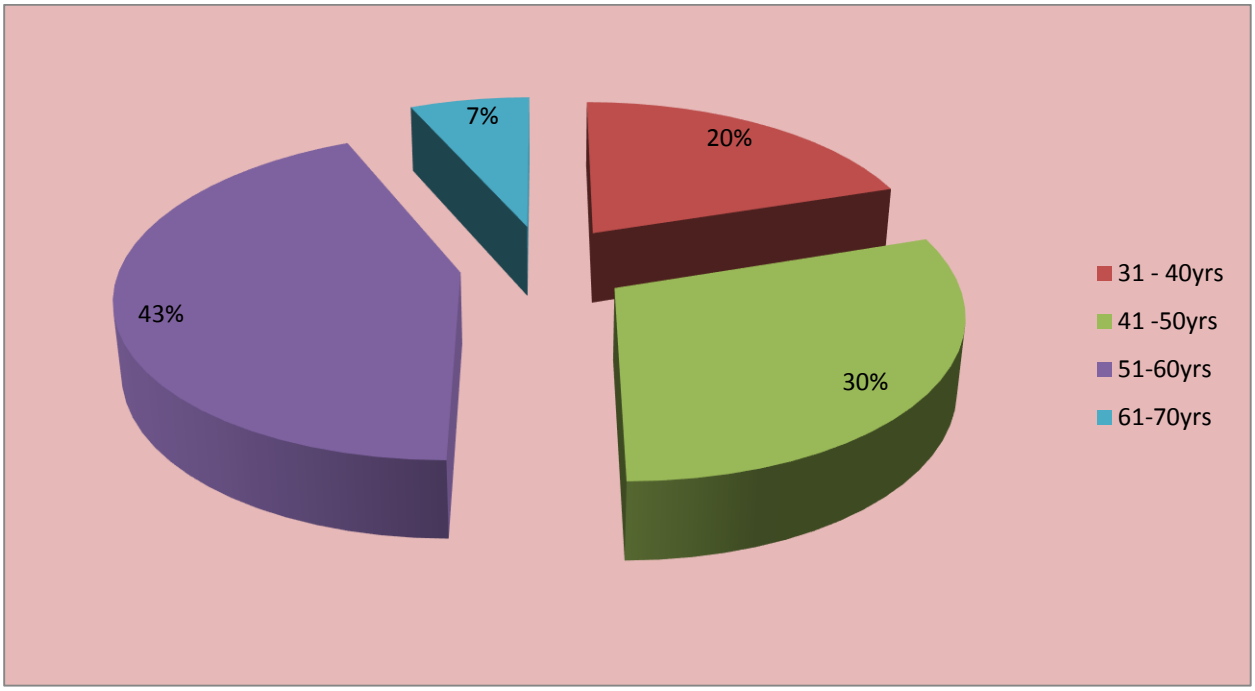
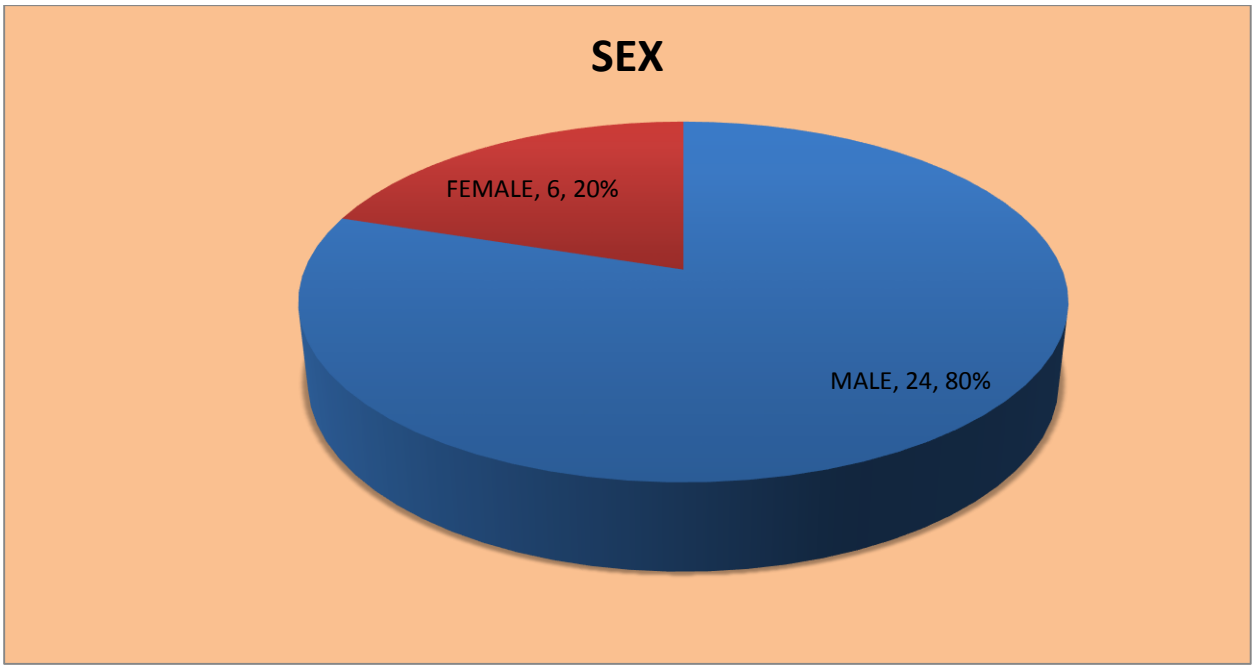


Figure no: 4, Gender distribution of the study population



GENDER:

The gender distribution in the study population is dominated by the exposure of risk factors tobacco, alcohol etc. Since male population are more frequent for exposure, this study as 24 male patients followed by 6 female patients. (figure no :4).

Table no: 5, GENDER DISTRIBUTION OF THE STUDY POPULATION

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	24	80%
FEMALE	6	20%

PERFORMANCE STATUS:

All patients in this study had a general performance status of ECOG (Eastern Cooperative Oncology Group)grade 0 or 1.(figure no:5)

Table no:6, ECOG performance status

ECOG	NO.OF PATIENTS	PERCENTAGE
ECOG 0	18	60%
ECOG 1	12	40%

HABITS:

In the natural history of head and neck cancer, habits /addictions of the patients to tobacco, alcohol plays a major role. In this study, as expected, majority of the patients had habit of both tobacco (smoking and smokeless) and alcohol

Table no: 7, Habits / addictions in the study population.

HABITS	NO.OF PATIENTS	PERCENTAGE
TOBACCO(SMOKING)	19	63%
TOBACCO(SMOKELESS)	11	36%
ALCOHOL	16	53%
NONE	4	13%

SYMPTOMS AND SIGNS:

Among the study patients the most common presenting symptom was dysphagia followed by ulcer/growth.(figure no:6)

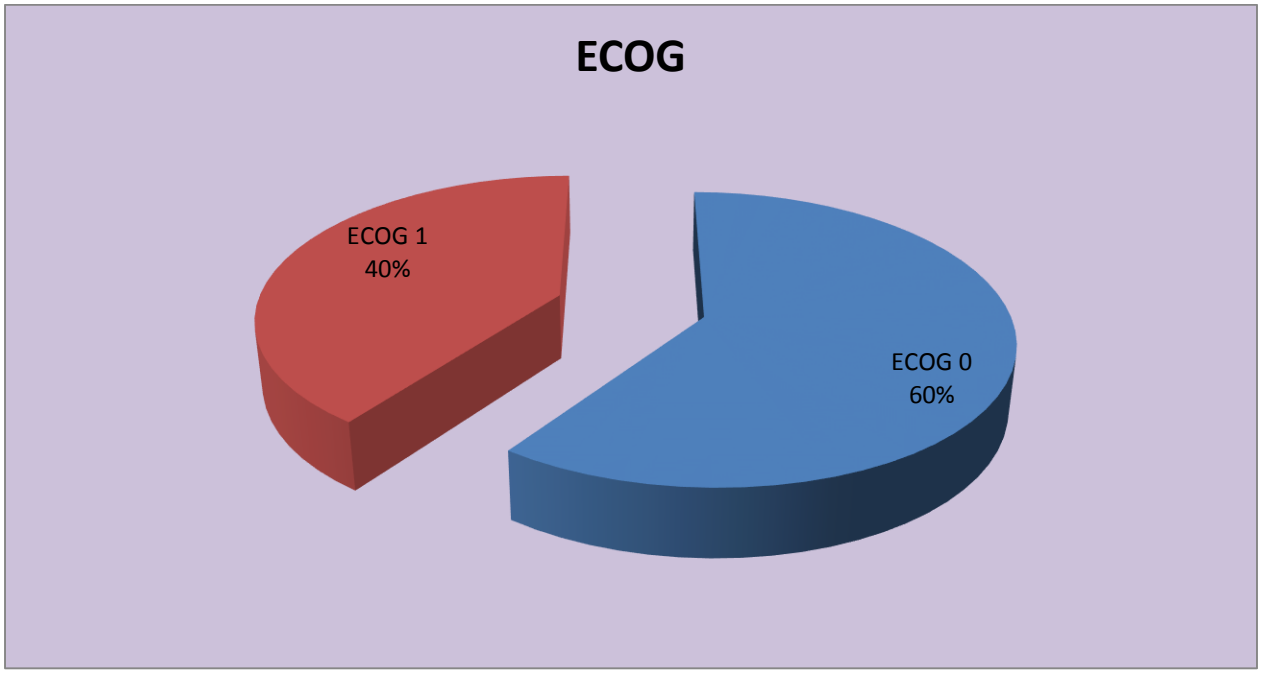
Table no: 8, Symptoms/Signs

PRESENTING SYMPTOMS/SIGNS	NUMBER	PERCENTAGE
PAIN	12	40%
ULCER/GROWTH	16	53%
DYSPHAGIA	18	60%
ODYNOPHAGIA	12	40%
NECK SWELLING	7	23%
VOICE CHANGE	4	13%

PRIMARY SITE:

In this study Oropharynx were 9 patients, followed by Hypopharynx 8 patients then Oral cavity 7 patients and larynx 6 patients.(figure no:7)

Figure no:5, ECOG performance status



Figureno:6, Symptoms and signs

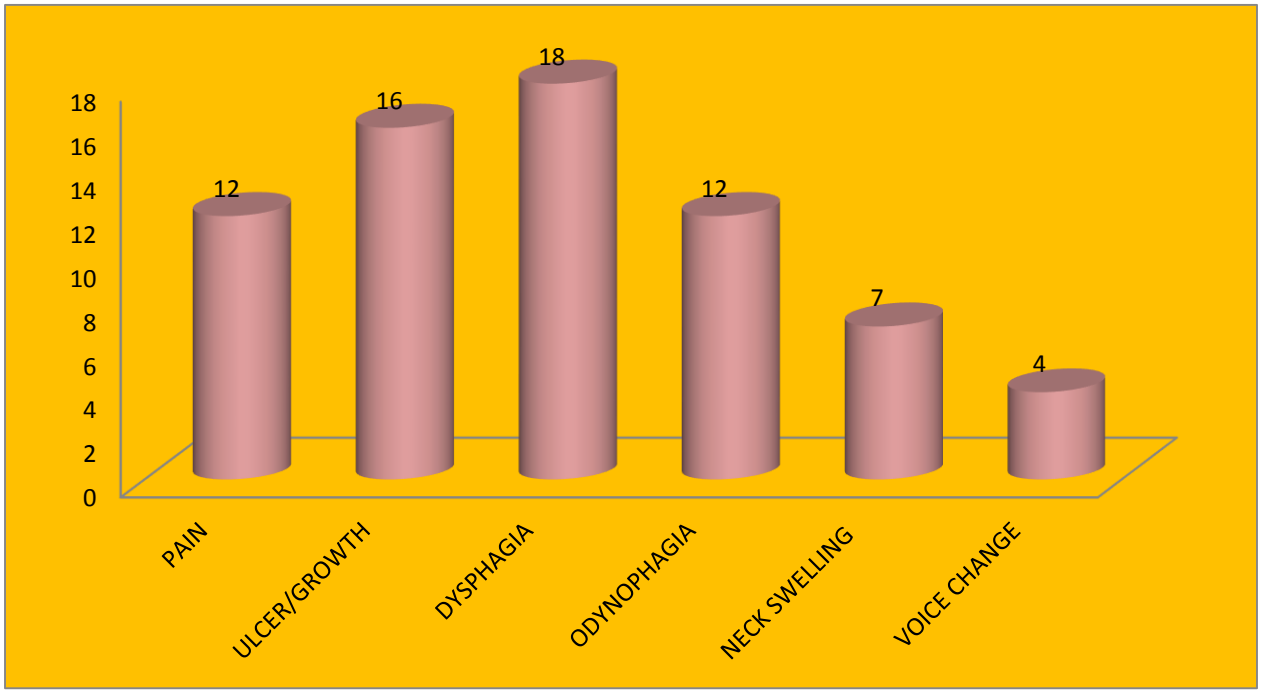


Table no:9, Primary site

PRIMARY SITE	NUMBER	PERCENTAGE
ORAL CAVITY	7	23.3%
OROPHARYNX	9	30%
HYPOPHARYNX	8	26.67%
LARYNX	6	20%

SUBSITE ANALYSIS:

In the subsite anaylsis Tongue (antr 2/3 and posterior 1/3) are equal in number.(figure no: 8)

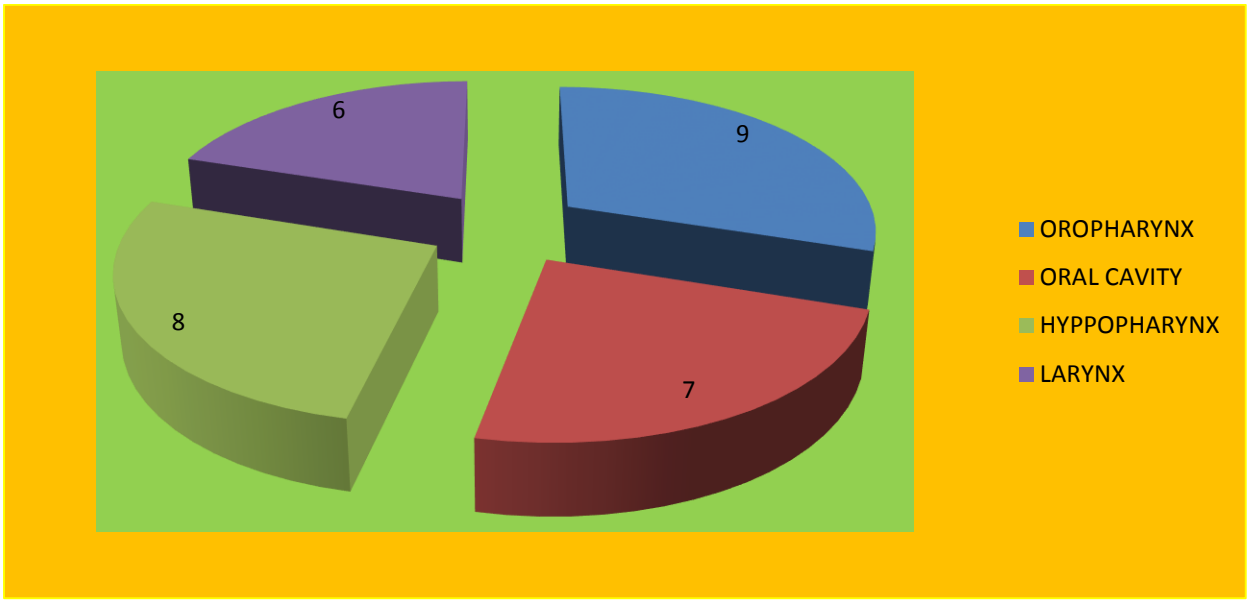
Table no: 10, subsite analysis

SUBSITE	NUMBER	PERCENTAGE
TONGUE	6	20%
POSTERIOR 1/3 TONGUE	6	20%
RMT	1	3.33%
TONSIL	3	10%
POST CRICOID	3	10%
PYRIFORM SINUS	5	16%
SUPRAGLOTTIS	6	20%

TUMOR STAGE:

This study included only locally advanced head and neck cancer T stage with T2 (with node positive), T3, T4a .(figure no:9)

Figure no:7, Site distribution of the study population



Figureno:8,Subsite Analysis

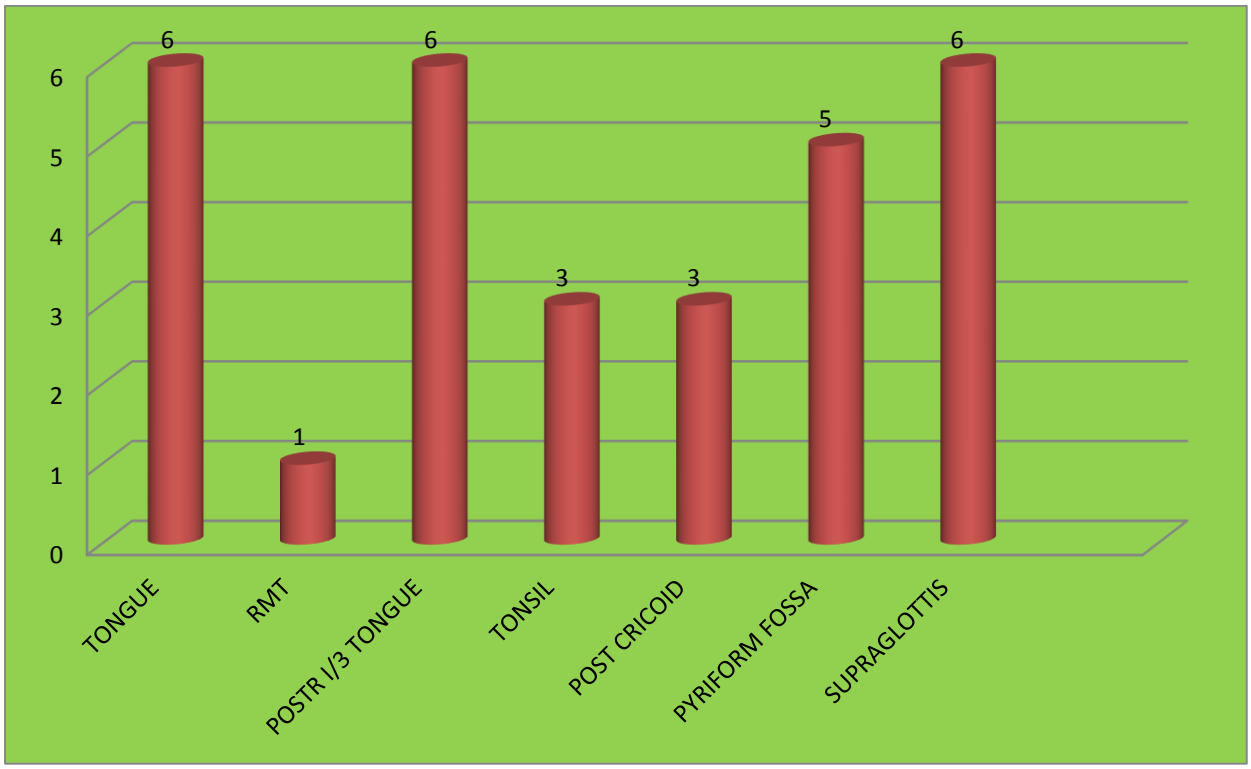


Table no:11, Tumor stage

T STAGE	NUMBER	PERCENTAGE
T1	0	0
T2	2	6%
T3	16	53%
T4	12	40%

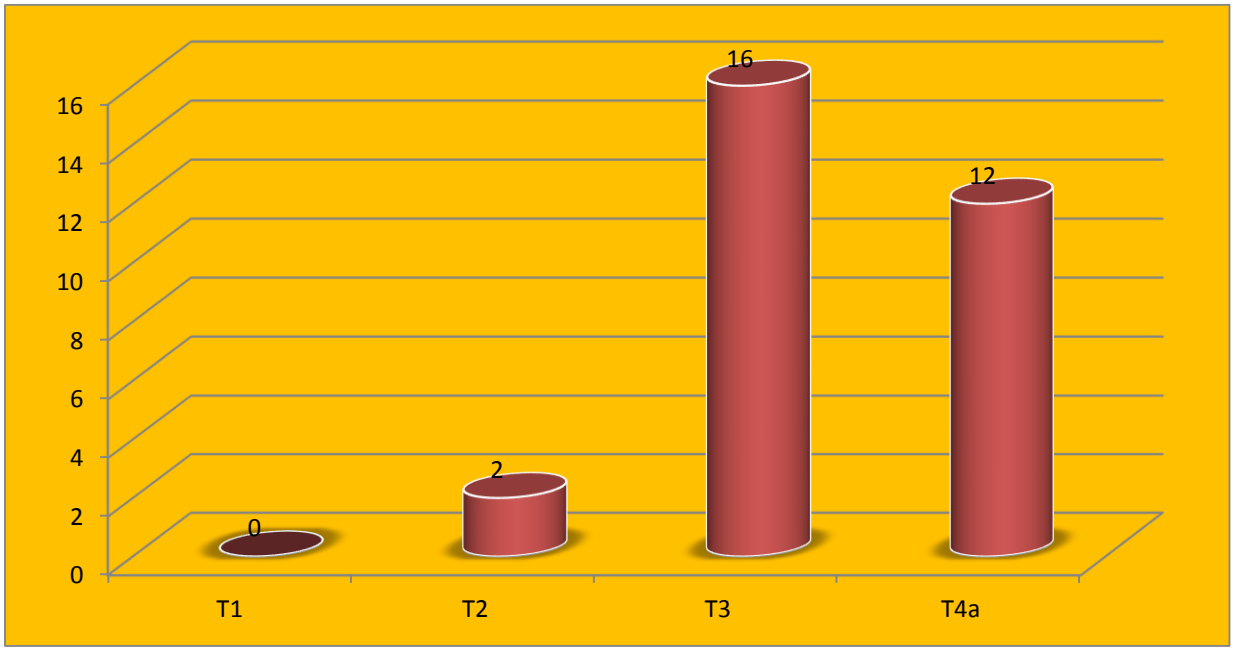
NODAL STAGE:

Nodal staging 60% of the patients as N2, only 3% (only one patient) had N3 disease.(figure no:10)

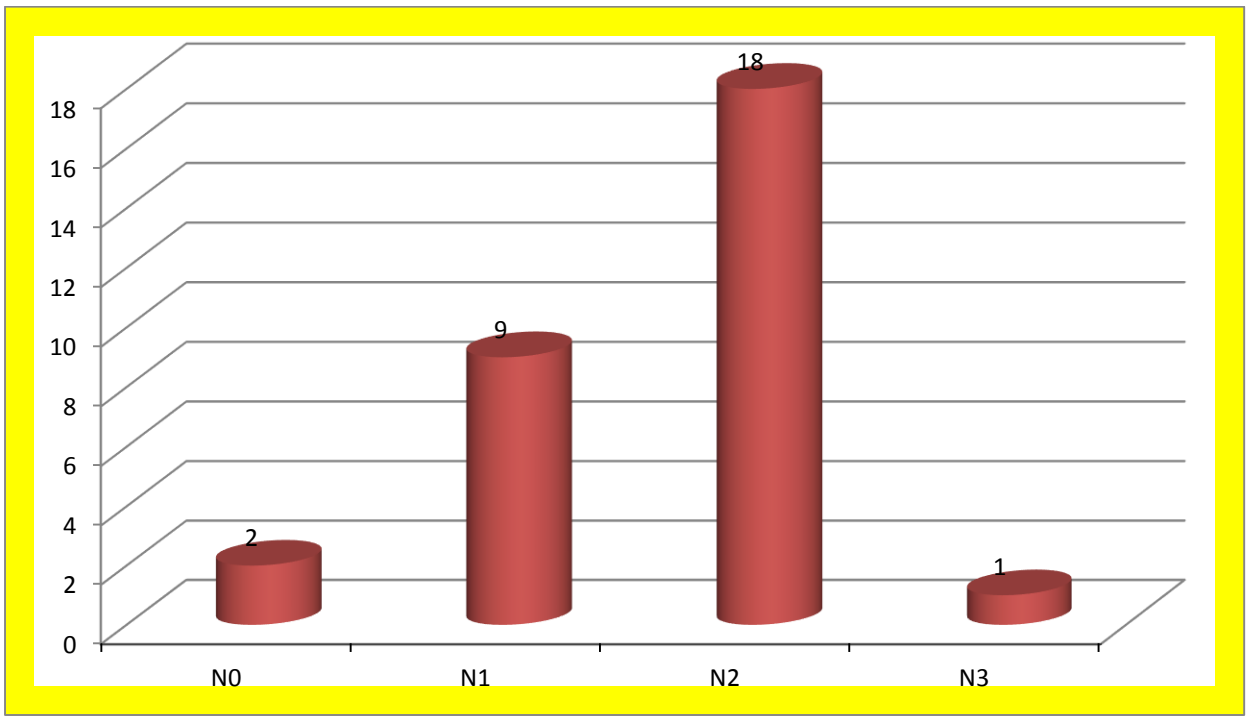
Table no: 12, Nodal stage

NODAL STAGE	NUMBER	PERCENTAGE
N0	2	6%
N1	9	30%
N2	18	60%
N3	1	3%

Figure no: 9, T stage in the study population



Figureno:10,Nodal stage in the study population



STAGE GROUPING OF THE STUDY SAMPLE:

The staging grouping was done according to AJCC 7th edition. As our general population usually present late to the hospital most of our patients were in stage IV a and only one patient in stage IV b (T3N3M0). (figure no:11)

Table no: 13, stage grouping

STAGE GROUPING	NUMBER	PERCENTAGE
STAGE III	7	23.33%
STAGE IV A	22	73.33%
STAGE IV B	1	3.33%

HISTOLOGICAL DIFFERENTIATION:

Most of the patients in the study belonged to moderately differentiated histology followed by poorly differentiated.

TABLE NO:14, Histological differentiation

HISTOLOGICAL DIFFERENTIATION	**NUMBER**	**PERCENTAGE**
WELL DIFFERENTIATION	7	23.33%
MODERATELY DIFFERENTIATED	17	56.66%
POORLY DIFFERENTIATED	6	20%

TREATMENT RESULTS:

All 30 patients completed the treatment protocol and were assessed at the end of 4-6 weeks. The evaluation was done clinically, which included ENT (Ear, Nose, Throat) examination with indirect laryngoscopy and direct laryngoscopy, and CT imaging (plain and contrast). The RECIST 1.1 criteria were used to classify the response type into a complete response, partial response, static or progressive disease.

Figure no: 11, Stage grouping

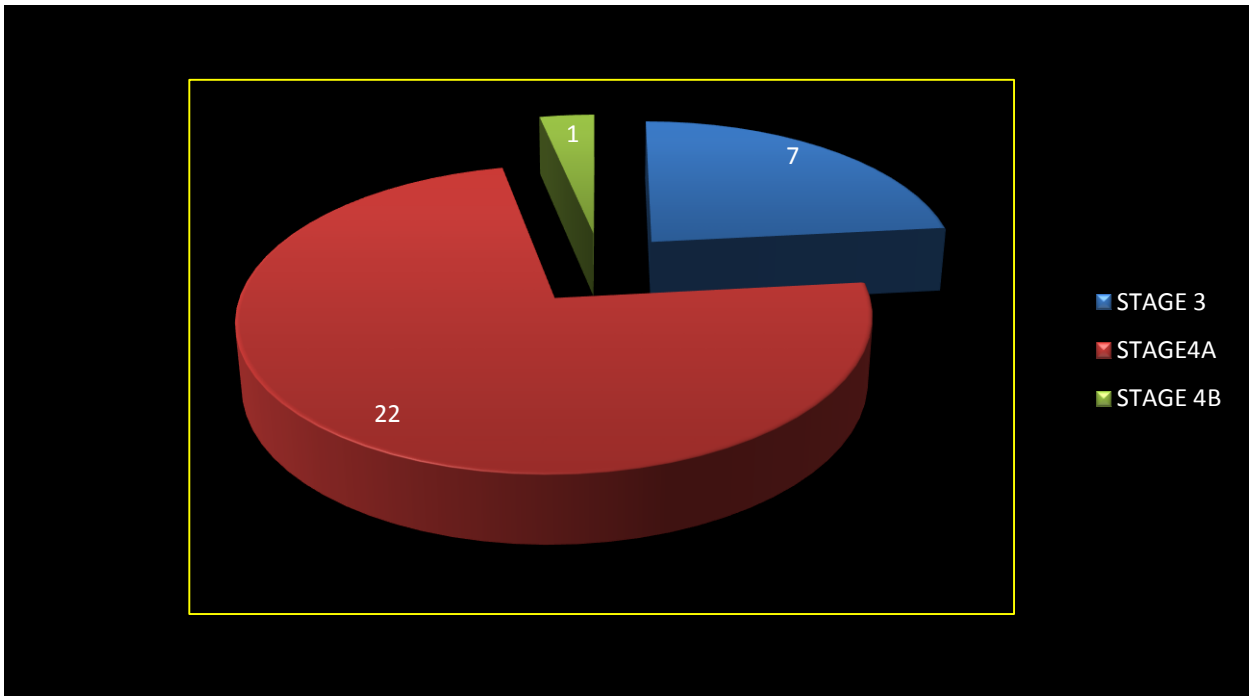
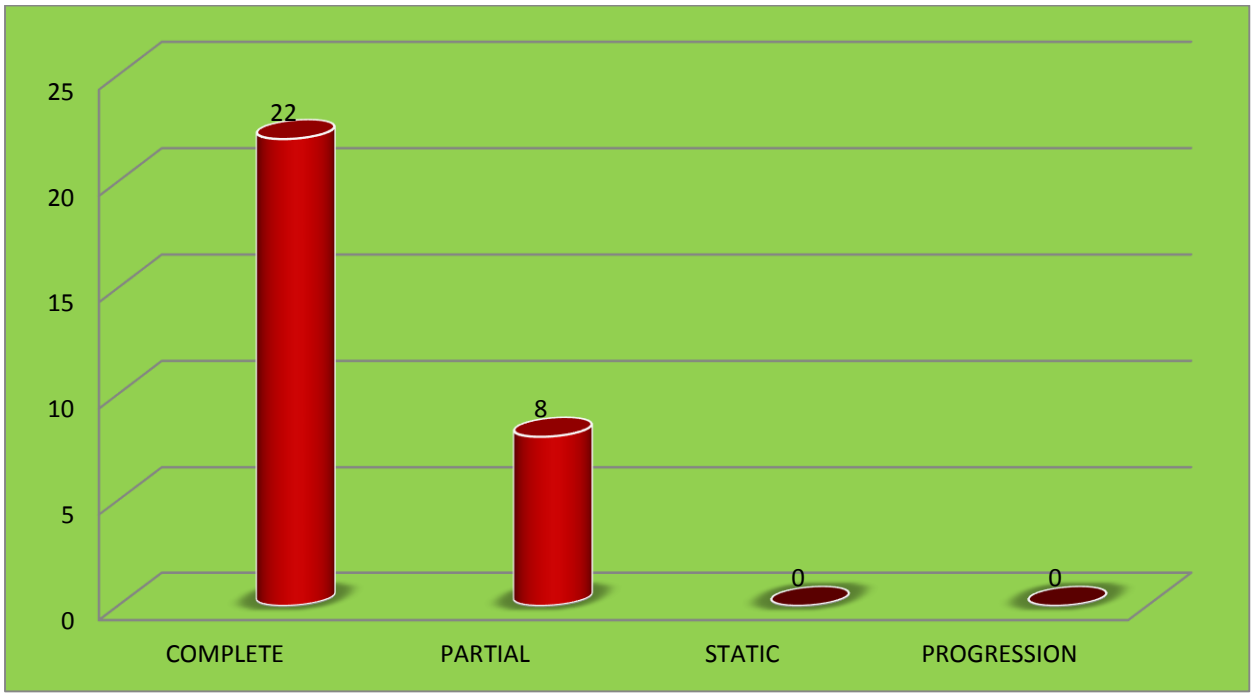


Figure no:12, Treatment results - Response



RESPONSE RESULTS:

In this study 73% of the patients had complete response and 27% had partial response. There was no static response or progression in the study. (figure no:12)

Table no:15, Response results

RESPONSE	NUMBER	PERCENTAGE
COMPLETE RESPONSE	22	73.33%
PARTIAL PRESPONSE	8	26.66%
STATIC RESPONSE	0	0
PROGRESSION	0	0

SUBSET ANALYSIS:

All the patient characteristics were analyzed for response at the end of the treatment. The results are stated in percentage. Due to the single arm analysis and small sample size of 30 patients, the study tests of significance cannot be relied on.

SITE Vs RESPONSE:

In this study Oropharynx had highest complete response for 7 patients, followed by larynx all 6 patients had complete response. Partial response was equal in both Hypopharynx and oral cavity.(figure no:13)

Table no:16, Site Vs Response

SITE	COMPLETE RESPONSE	PARTIAL RESPONSE
ORALCAVITY	4(57%)	3(42.85%)
OROPHARYNX	7(77.8%)	2(22.2%)
HYPOPHARYNX	5(62.5%)	3(37.5%)
LARYNX	6(100%)	0

TUMOR STAGE Vs RESPONSE:

Out of the 16 T3 lesions, 12 patients had complete response whereas out of the 12 T4a patients only 8 had complete response. This shows the advanced nature of the disease.(figure no: 14)

Figure no:13, Site Vs Response

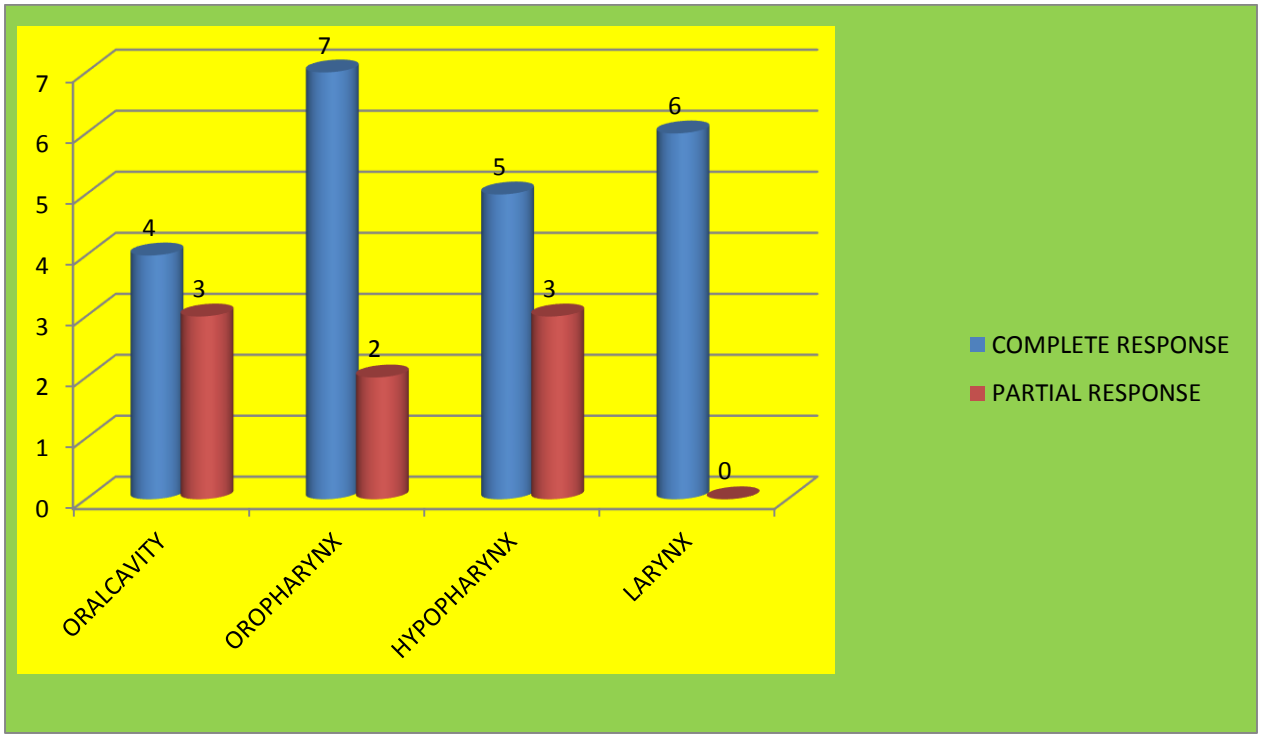


Figure no:14, T stage Vs Response

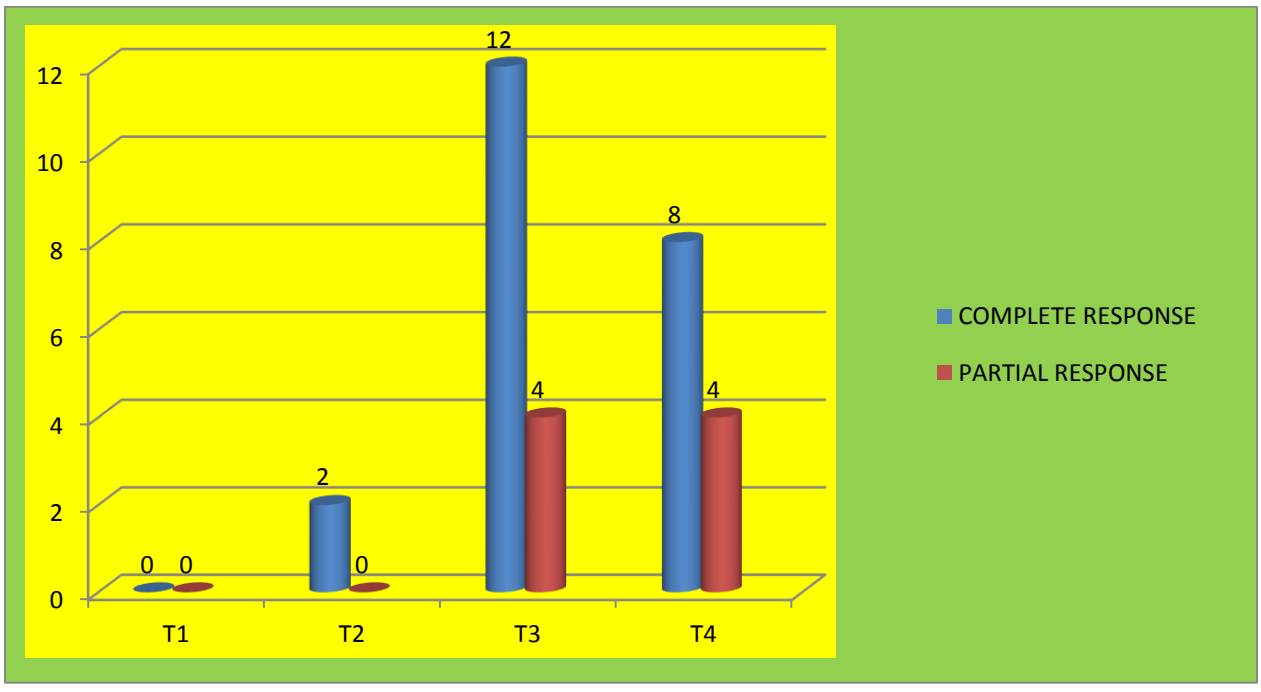


Table no: 17, Tumor Stage Vs Response

TUMOR STAGE	COMPLETE RESPONSE	PARTIAL RESPONSE
T1	0	0
T2	2(6%)	0
T3	12(40%)	4(13.34%)
T4	8(26.67%)	4(13.34%)

NODAL STAGE Vs RESPONSE:

All patients with N1, N2a, N2b nodes had complete response. Out of the 13 patients with N2c nodes 9 had complete response only 4 patients had partial response. Only one patient had N3 node with partial response.(figure no:15)

Table no:18, Nodal Stage Vs Response

NODAL STAGE	COMPLETE RESPONSE	PARTIAL RESPONSE
NO	2(6.66%)	0
N1	9(30%)	0
N2a	2(6.66%)	0
N2b	3(10%)	0
N2c	10(33.33%)	3(10%)
N3	0	1(3.33%)

HISTOLOGICAL DIFFERENTIATION Vs RESPONSE:

As already mentioned maximum numbers of the patients in our study were moderately differentiated; in which 12 patients had complete response and 5 had partial response. All poorly differentiated cancer had complete response. Out of seven well differentiated tumors only 4 had complete, this is lower when compared to the other two differentiations. (Figure no:16)

Figure no :15, Nodal stage vs Response

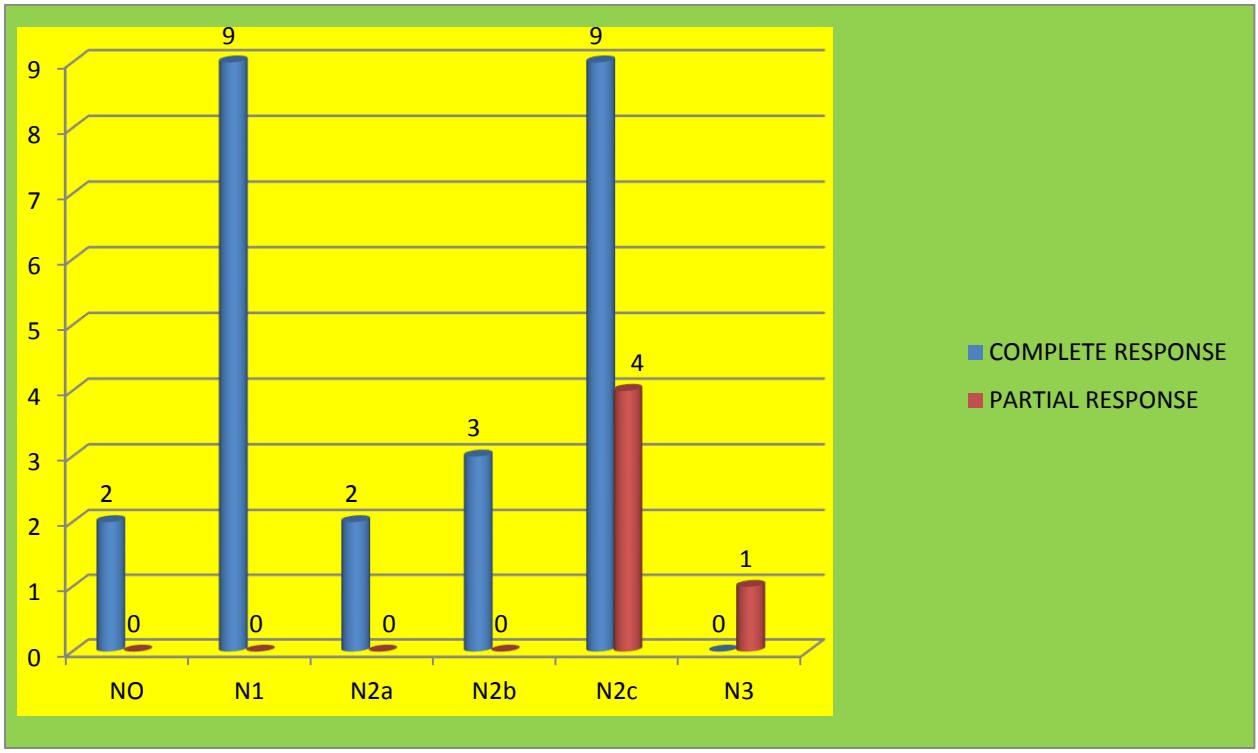


Figure no: 16, Histologic differentiation Vs Response

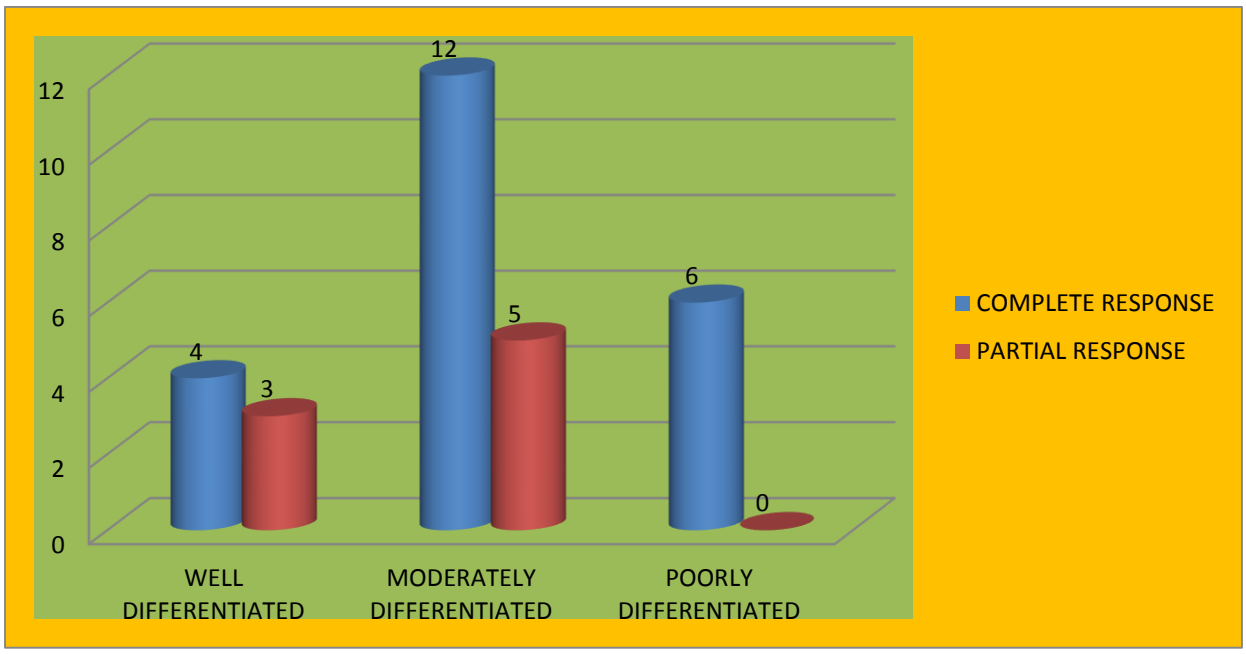


Table no: 19, Histological differentiation Vs response.

HISTOLOGIC DIFFERENTIATION	COMPLETE RESPONSE	PARTIAL RESPONSE
WELL DIFFERENTIATED	4(57.1%)	3(42.85%)
MODERATELY DIFFERENTIATED	12(70.58%)	5(29.41%)
POORLY DIFFERENTIATED	6(100%)	0

PERFORMANCE STATUS Vs RESPONSE:

The ECOG performance status among the study patients did not show much difference in the response rates, as the study patients are in the ECOG 0 OR 1.

Table no: 20, ECOG Vs Response

ECOG	COMPLETE RESPONSE	PARTIAL RESPONSE
0	13(43.33%)	5(16.66%)
1	9(30%)	3(10%)

PRIMARY AND NODAL SITES – DIFFERENTIAL RESPONSE:

In this study the complete response rate in the primary site was 73% whereas in that of the nodal region was 87%.(figure no:17,18)

OTHER FACTORS AFFECTING RESPONSE:

AGE:

In this study people aged less than 50yrs were 15 patients out of them 12(80%) had complete response. In case of above 50yrs there were 15 patients, in which only 66% had complete response.

Table no: 21, Age Vs Response

AGE GROUP	COMPLETE RESPONSE	PARTIAL RESPONSE
31-40Yrs	5(83.33%)	1(16.66%)
41-50Yrs	7(77.77%)	2(22.22%)
51-60Yrs	8(61.5%)	5(38.4%)
61-70Yrs	2(100%)	0

Figure no: 17, Response in the Primary

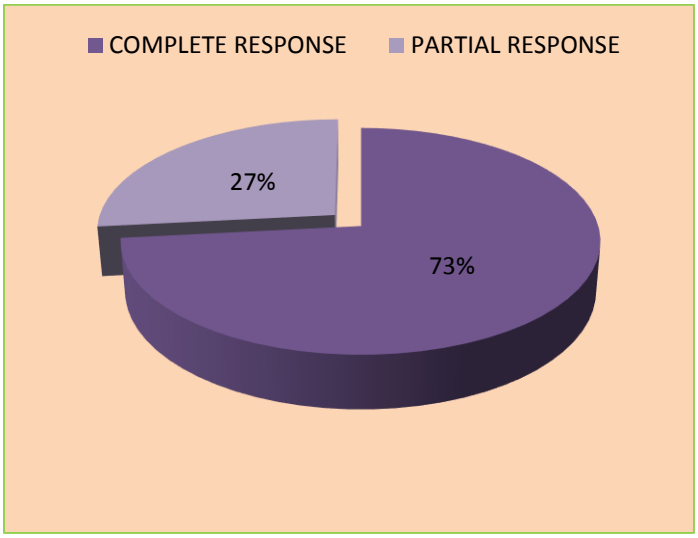


Figure no:18, Response in the Nodes

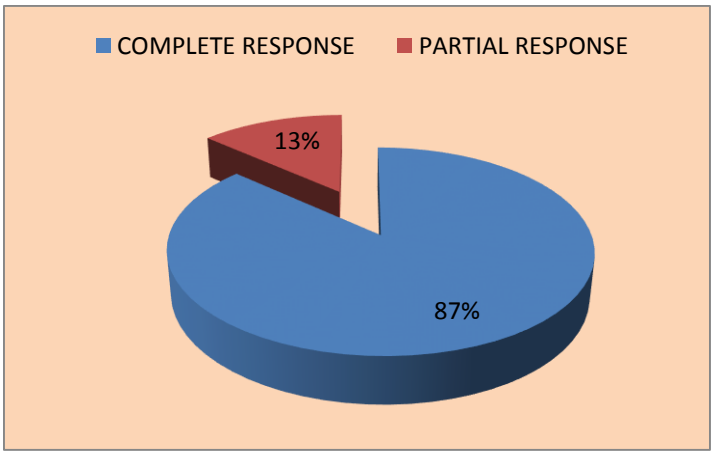
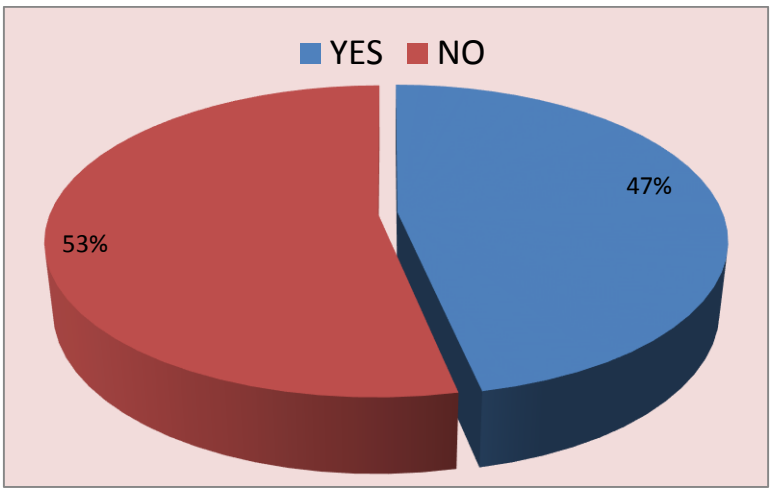


Figure no: 19, Treatment delay



GENDER Vs RESPONSE:

As the male population dominated the study 75% of the males had complete response in contrast to 66% of the females. As the male and female ratio was not equivalent it cannot be considered as significant.

STAGE Vs RESPONSE:

The complete response in Stage IV was 69% but the partial response was 30% which is high compared to Stage III partial response 14%. This is due to the fact that Stage IV disease is infiltrative and extensively spreading.

Table no :22, Stage Vs Response

STAGE	COMPLETE RESPONSE	PARTIAL RESPONSE
STAGE III	6(86%)	1(14.2%)
STAGE IV	16(69.5%)	7(30.4%)

TREATMENT BREAK Vs RESPONSE:

Treatment delay due to toxicities which caused prolongation of overall treatment time was analyzed for response. There was treatment delay in 47% of the patients compared to 53% who proceeded without

delay in overall treatment time. Among the 47% of the patients, most of the patients had 1-3 days treatment break had 83% complete response whereas only 62.5% had complete in case of treatment break for 4 days or more.(figure no:19,20)

Though there was treatment break all patient chemoradiation.

Table no: 23, Treatment break Vs Response

TREATMENT BREAK	**NUMBER**	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**
1-3 DAYS	6	5(83.33%)	1(16.67%)
$\geq$ 4DAYS	8	5(62.5%)	3(37.5%)

TREATMENT RELATED ACUTE TOXICITIES:

ACUTE LOCAL TOXICITY:

Acute local toxicity is done by RTOG Acute morbidity scoring criteria.(Table 20, figure no:21)

SKIN REACTION:

In this study 77% of the patients had Grade 1 skin reactions in the form of dry desquamation, decreased sweating. Another 16% had patchy

moist desquamation whereas only 6% of the patient had grade 3 confluent moist desquamation.

MUCOSITIS:

As expected there was high incidence of mucositis in this study. Nearly 40% of the study population developed grade 2 reactions in the form patchy mucositis. Also 16% had grade 3 confluent mucositis but there was grade 4 mucositis in 6% of the patients which required treatment break and supportive measures with analgesics, strict oral hygiene, mouth wash with alcohol free antibacterial solution.

Also Inj.Dexamethasone 8mg i.v. bid was given for 4-5 days.

SALIVARY GLAND /XEROSTOMIA:

The salivary gland toxicity in the form of xerostomia is usually managed with commercially available artificial salivary agents.73% of the patients had grade1 xerostomia with complaints like dry mouth and slightly altered taste sensation. Some 16% patients developed complete dryness, sticky saliva as grade 2 toxicity reaction.

PHARYNGITIS:

The patients with grade 2 and grade 3 dysphagia were given Ryles tube feeding and adequate nutrition was maintained. If needed

Figureno:20 Response Vs Treatment break

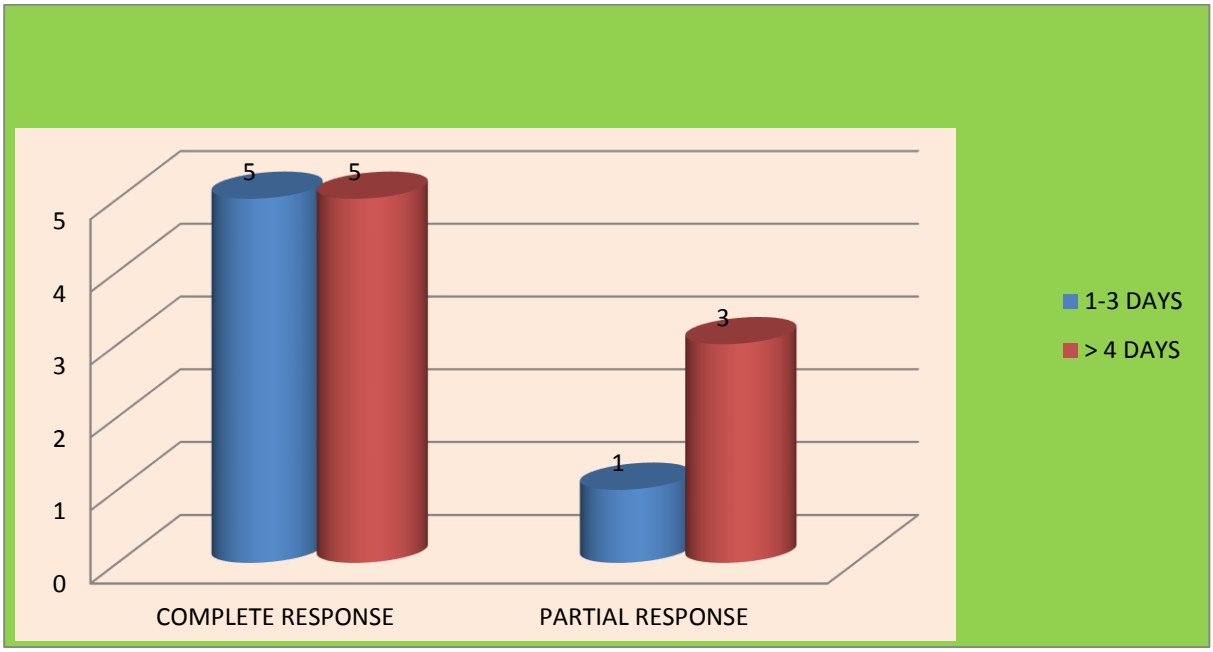
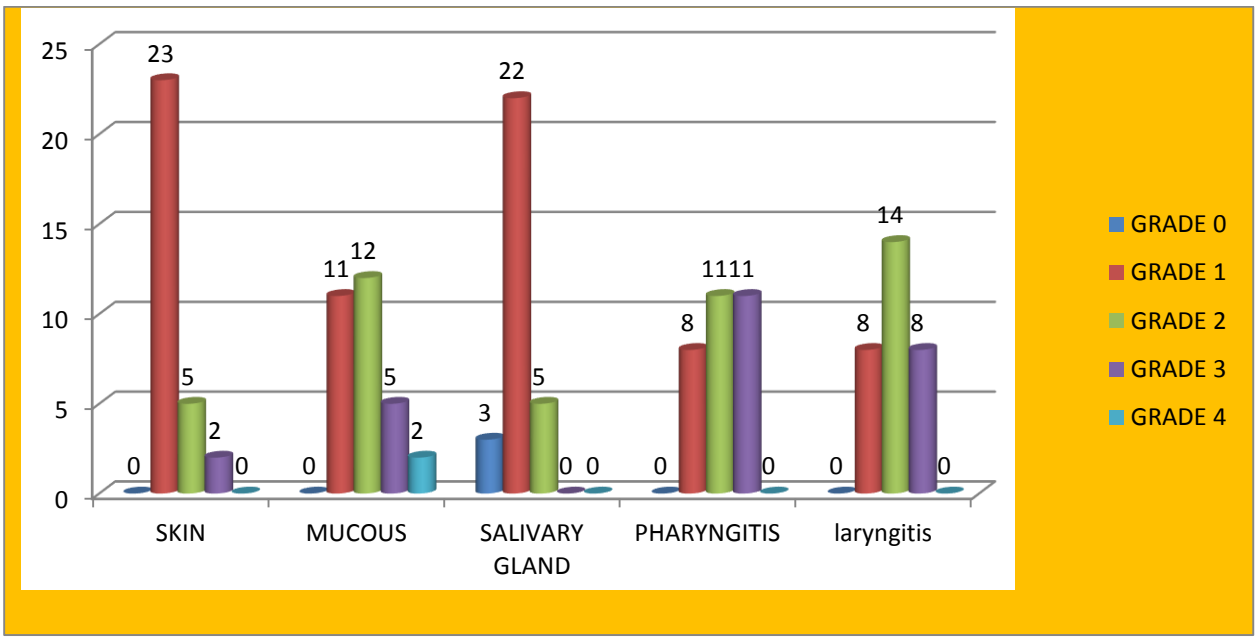


Figure no: 21,Acute toxicity



intravenous fluids and parentral nutrition were given. Only 26% of the patients had grade 1 dysphagia remaining had either grade 2 or 3.

LARYNGITIS:

Grade 2 Laryngitis developed in 46% of the patients who had hoarseness of voice and constant cough requiring cough syrup. Grade 3 laryngitis developed in 26% of the patients they had only whispered speech. Remaing had grade 1 toxicity which subsided on its own.

Table no:24, Acute toxicity

ACUTE TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
SKIN REACTIONS	0	23 (76.66%)	5 (16.66%)	2 (6.66%)	0	0
MUCOSITIS	0	11 (36.66%)	12 (40%)	5 (16.67%)	2 (6.67%)	0
SALIVARY GLAND	3 (10%)	22 (73.3%)	5 (16.67%)	0	0	0
PHARYNGITIS/ DYSPHAGIA	0	8 (26.67%)	11 (36.67%)	11 (36.67%)	0	0
LARYNGITIS	0	8 (26.67%)	14 (46.67%)	8 (26.67%)	0	0

SYSTEMIC TOXICITY:

The treatment related systemic toxicity was assessed with CTCAE V 4.03 and presented (Table no: 21, figure no:22)

NAUSEA:

83% of the study population developed loss of appetite grade 1 nausea during their treatment course.13% of the developed grade 2 nausea.

VOMITING:

80% of the patients had grade 1(1 or 2 episode) of vomiting during chemotherapy mainly Cisplatin. Only 6% of the patients had grade 2(3 or 4 episodes) of vomiting managed by Oral Rehydration Salt and Inj.Ondansetroniv bid for 3 -5 days. Intravenous fluids were given whenever necessary.

DIARRHOEA:

Only 6% of the patients had grade 1 diarrhoea. Other than that none of the study patients had diarrhea. Mostly the grade 1 diarrhoea is self-limiting, anti-motility drugs like Tab. Loperamide was used when needed.

HAND FOOT SYNDROME:

The dose limiting toxicity of Capacitabine hand foot syndrome did not occur in any patients in this study.

Table no: 25,Systemic toxicity

TOXICITY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
NAUSEA	25 (83.33%)	4 (13.33%)	1 (3.33%)	0
VOMITTING	24 (80%)	6 (20%)	0	0
DIAHORREA	2 (6.66%)	0	0	0

HEMATOLOGICAL TOXICITY:

ANAEMIA:

In this study 18 patients had hemoglobin >11g % and 26% had reduction in their Hb levels during treatment between 9.5 -11g%. 13% of the patients developed reduction in Hb levels to below 9g% and required Packed cell transfusion.(figure no:23)

Table no: 26**,** Anemia

ANEMIA	NUMBER	PERCENTAGE
GRADE 0	18	60%
GRADE 1	8	26.67%
GRADE 2	4	13.33%
GRADE 3	0	0
GRADE 4	0	0

Figureno:22,Systemic toxicity

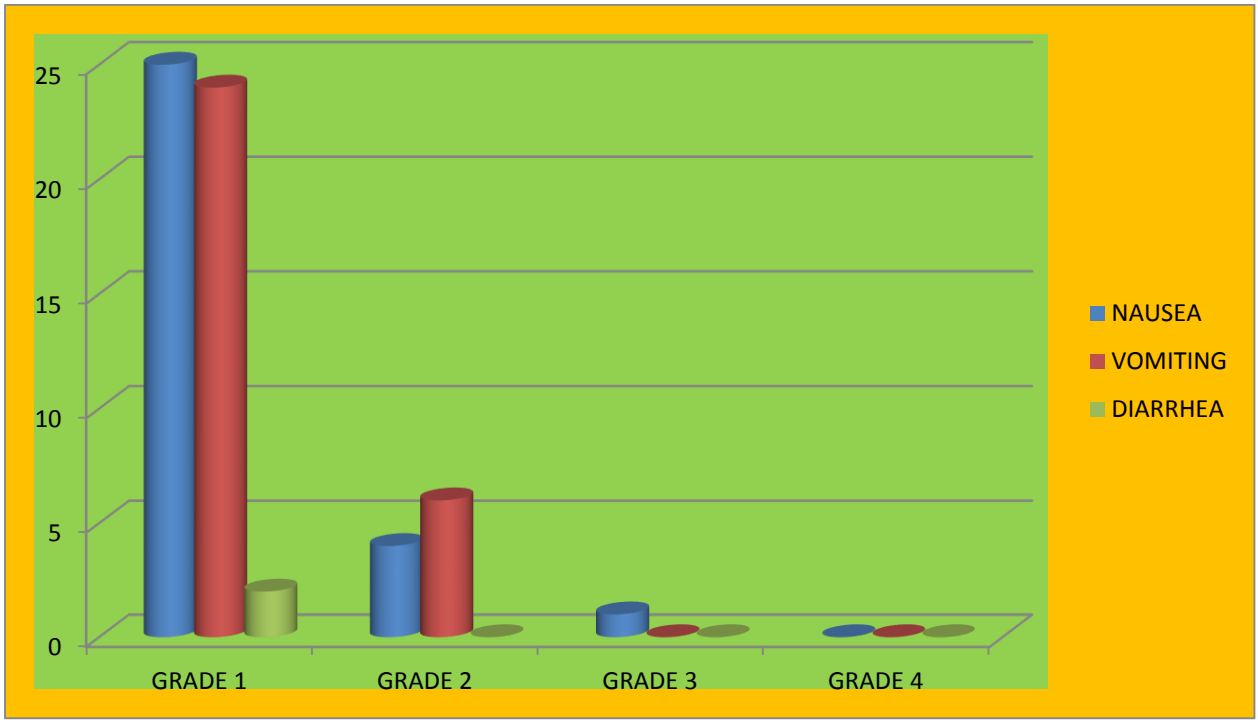
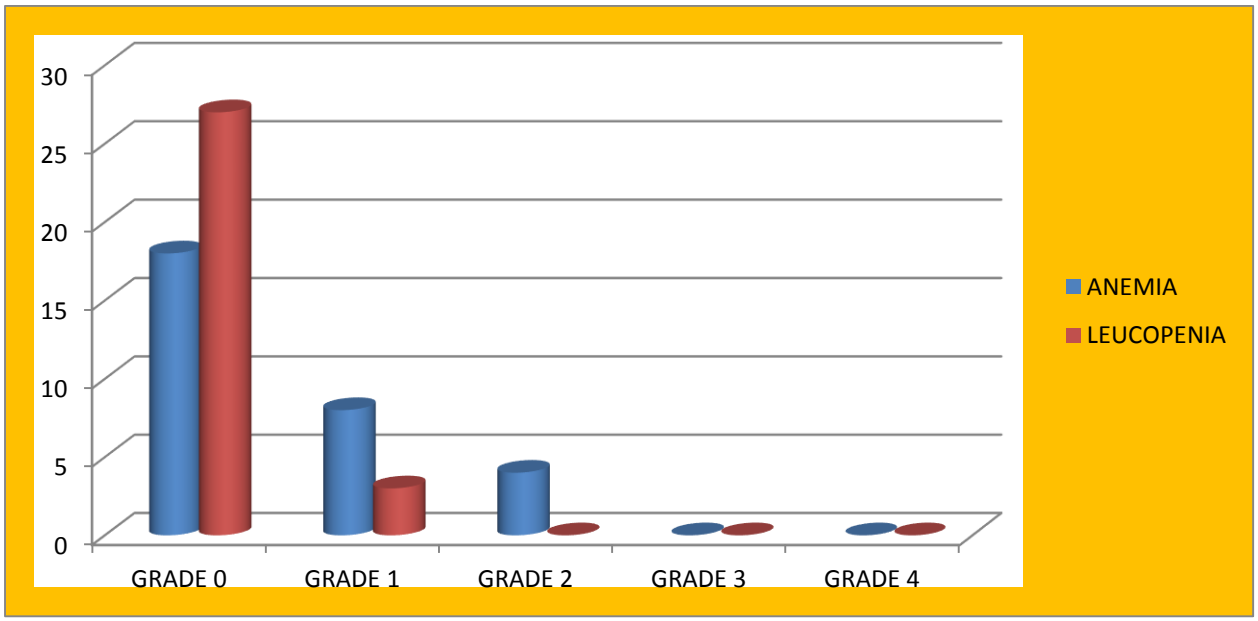


Figure no: 23, Hematological Toxicity



LEUCOPENIA:

About 27 patients had WBC count >4000 during entire treatment. Only 3 patients developed reduction in WBC count level during chemotherapy between 3000 – 4000 grade1 Leucopenia. This can be attributed to the drug capectiabine.

NEUTROPENIA:

There was no neutrophil count reduction in the study.

THROMBOCYTOPENIA:

None of the study patients developed thrombocytopenia.

RENAL TOXICITY:

All patients had normal renal function tests. Hence none of the patient developed renal toxicity.

DISCUSSION

DISCUSSION

The head and neck cancer census incidence is increasing in the present decade. Mainly in India, due to the habit and addiction towards tobacco in smoked form like cigarettes or beedi also in smokeless forms like pan, kurkhaetc plays a major causative effect. As the youngster's exposure to these agents increase, there is rise in cancer incidence, mainly head and neck cancer.

As the head and neck cancer affects the quality of life in patients due to disfigurement, dysphagia, hoarseness of voice etc. Patients in our country present in advanced stage due to lack of awareness, illiteracy, poor socioeconomic status. This gives them very limited treatment options.

Many trials have been published in different radiation and chemotherapy combinations in head and neck cancer. The standard of care is proved to be concurrent chemoradiation with radiation 66-70 Gy in 33 – 35 fractions in two Gy per fraction 5 days a week along with chemotherapy Inj. Cisplatin 100mg /m^2 in D1, 22 and 43.

The drawback in this regimen is Cisplatin in high dose is not tolerated by most of the people and toxicity is high. Thus the dose of Cisplatin is given by split weekly low dose in many institution, this regimen as the same efficacy as the three weekly regimen with much less toxicity. MACHNC trial also states that the cumulative dose cisplatin should more than 200mg/m^2.

Various concurrent chemoradiation trials as proven the benefit of weekly cisplatin single agent as equivalent results. Even a study done in our department Barnard institute of Radiology and Radiotherapy also showed that weekly cisplatin and three weekly cisplatin both as similar treatment results except that the toxicity in weekly is much less compared to the three weekly regimen.

Table no: 27

CISPLATIN WITH RADIATION	COMPLETE RESPONSE RATE IN %	PARTIAL RESPONSE RATE IN %
THREE WEEKLY	64	36
WEEKLY	62	38

Thus single agent weekly cisplatin is an accepted regimen.

COMBINATION CHEMOTHERAPY:

Though MACHNC – Meta analysis of chemoradiation in head and neck cancer suggests that there is no added benefit with combination chemotherapy over single agent Cisplatin but toxicity as increased. But it also showed that combination of Cisplatin based regimens has better results than other single agent drugs.

Based on all these data combination of Cisplatin and 5 Fluorouracil has been widely used in locally advanced head and neck cancer along with radiation.

The dose of Cisplatin and 5 FU used in this combination are 100mg/m^2 and 1000g/m^2 continuous infusion for 5 days in the interval of 21 days. The demerits of this combination are high mucositis and diarrhea produced by 5FU resulted in toxicity and treatment breaks. To overcome this toxicity a study done in a Korea institute tried weekly combination of Cisplatin and 5FU. In this study they used weekly Cisplatin 20mg/m^2along with 5FU 750mg/m^2,concurrently with radiation dose of 70Gy/35 fractions. There were 38% grade3 toxicities. Also the complete response and partial response in this study was 41% and 50%.the OS at 1yr and 2yr was 69% and 66% respectively. Though the authors state that this as a feasible study with high compliance, this study as low complete

response rate of only 41%. This is due to the fact that total cumulative dose of cisplatin was less than 200mg/m^2. Also study population could tolerate weekly 5FU, increased toxicities lead to treatment breaks.[78]

CAPECITABINE:

Capecitabine oral prodrug of 5FU, antimetabolite acts as a potent radiosensitizer. Capecitabine is used as a single agent in head and neck squamous cell carcinoma. Its role in metastatic and recurrent head and neck cancer is well established. Capecitabine as a single agent concurrently with radiation in recent trials and it as proved its superior efficacy in the form of higher complete response, less toxicity compared to weekly cisplatin.

But the dose of Capecitabine when used concurrently is reduced to 500mg/m^2 twice daily. Also Capecitabine acts as a targeted therapy with its rate limiting enzyme thymidine phosphorylase expressed at higher levels in tumors with hypoxia, acidosis and low pH. This is the condition in most of the solid tumors especially head and neck cancers. Thus the concentration of Capecitabine in tumor cell is 2.9 times higher than the normal tissues, reducing normal tissue toxicity. This is proved in various pharmacokinetic studies and trials with only Capecitabine with conventional radiation.

Cisplatin and Capecitabine have been used in three weekly regimens in various trials and the efficacy of this regimen is less toxic compared to cisplatin and 5FU. The response rates of this regimen are also better than cisplatin and 5FU. Though it is less toxic compared to cisplatin and 5FU, there was higher grade 3 and 4 toxicities and treatment breaks which resulted in poor compliance of the patients. Also despite the use various chemotherapy regimens in head and neck the loco regional failure is a complicated issue.

This present study was formulated with the idea of using potent chemotherapy drug with radiosensitization which might have a better toxicity profile, better loco regional control with good response rates.

This study of concurrent chemoradiation with weekly cisplatin and Capecitabine has shown better locoregional control rates with complete response rates of 73% and partial response rate of 27% this is higher compared to weekly cisplatin single agent trial which as complete response rate of 62% conducted in our department.

There was no static or progressive disease in this study. Also all patients completed their entire chemoradiation schedule. Other trials using cisplatin and Capecitabine are already discussed.

Table no:28, Capecitabine trials

AUTHOR	RADIATION	CHEMOTHERAPY	RESPONSE/ TOXICITY
Sherif A. Raafat et al	66 – 70Gy in 2Gy per fraction,33-35 fractions	Cisplatin 30mg/m^2weekly Vs Capecitabine 500mg /m^2 twice daily	CR with cisplatin is 60% Vs Capecitabine as CR of 77% Toxicity – mucositis in 93% of Capecitabine group Vs 57% in cisplatin group.
JG Kim et al	70 Gy in 2 Gy per fraction.	cisplatin of 80 mg/m^2 on day 1 and oral capecitabine 825 mg/m^2 twice daily from day 1 to 14 at 3-week intervals	complete responses (78.4%) and partial responses (16.2%)Grade 3 mucositis in 67.6, dermatitis grade ¾ in24.3%. hand foot mouth syndrome in 2 patients.

SUBSET ANALYSIS:

In this present study the complete response was 73% and partial response was 27%.

Age at diagnosis had a significant effect on response outcome, people aged less than 50yrs 80% had complete response. In case of above 50yrs only 66% had complete response. This could be explained as young

age patients had good general condition, nutrition status and performance status.

The male population dominated the study with80%, this can be explained due to the habits of tobacco and alcohol in male patients. The response rate also higher in males with 75% had complete response in contrast to 66% of the females.

All patients in this study belonged to performance status ECOG 0 or 1. Both the group had more less equal response rates. So performance status wise significance in difference could not be made out.

As the site of primary tumor is considered Larynx as 100% CR (supraglottis) followed by oropharynx with CR 77% and Hypopharynx with CR 62.5%. the Cr in oral cavity was comparatively less of 57% with high partial response 42.5% compared to other sub sites. This can be explained due to the fact that Oral cavity lesions are well differentiated tumor, so their response to Chemo RT is inferior than moderately or poorly differentiated histology. This study also showed similar results with poorly differentiated high CR > moderately > well differentiated histology.

The response rate in the primary site and nodal region was different inn this study. At the primary site CR was 73% whereas in that of the nodal region was 87%. Also N3 disease showed only partial response.

The T4a lesion due to its extensive infiltrative lesions had 33% partial response compared to 25% partial response in T3 lesion. Though there is high partial response in T4a due to hypoxia, necrosis of tumor burden this is comparatively less in total partial response in which it accounts only 13%.

The primary objective of this study was to determine the locoregional control as discussed above. As the sample size was small, statistical analysis is questionable for its significance.

The secondary objective of this study is the toxicity assessment. As showed in trials cisplatin and Capecitabine in full dose three weekly schedules as grade 3 and 4 toxicity. But in this present we use weekly cisplatin and Capecitabine low dose continuously concurrent radiation showed manageable toxicity. Mucositis is usually increased in concurrent chemoradiation trials in same way this study also showed grade 2 mucositis 40%, grade 3-16% and grade 4- 6%. Grade 4 mucositis needed treatment to resolve and again proceeded with complete treatment. This is attributed to the additional effect of radiotherapy that too patients are

treated with Cobalt 60 and not in 3DCRT, IMRT. Also all patients had dermatitis grade 1 in 76.66% of patients and grade 3 in 6% of patients. These can be explained because of the radiosensitising effect of cisplatin and Capecitabine.

There was no Hand foot syndrome in the patients of this study. Nausea and vomiting was also grade 1 and self-limiting in most patients.

Also diarrhea major side effect of 5FU was seen in only 6% of patients. It was only grade 1 diarrhea and treated with antimotility drugs. There was no dehydration in any patients.

All patients were hydrated properly during chemoradiation and thus none of the patients had renal toxicity.

There wasn't any thrombocytopenia among study patients. There was only 10% of the patients had grade 1 Leucopenia and managed accordingly. Anemia grade 2 in 13.3% of patients and packed cell transfusion was given. Most of our patients are from low socioeconomic status, anemia may be explained due to nutritional deprivation.

There wasn't any treatment related deaths in this study.

Merits of this study:

- All patients had locally advanced head and neck squamous cell caracinoma, the treatment of choice is concurrent chemoradiation, was given.
- Optimal tumoricidal dose of 66Gy was administrated.
- Optimal dose of weekly cisplatin > 200mg/m^2 was achieved in all patients.
- Capecitabine toxicity of hand foot syndrome didn't occur in any patients.
- The chemotherapy in weekly schedule assisted to strict regular monitoring of toxicity reactions.
- Toxicities were manageable. No treatment related death occurred in this study. Toxicity were graded with RTOG Acute radiation morbidity scoring criteria and CTCAE version 4.03
- Response assessment was done after 4-6weeks of completion of chemoradiation, RECIST 1.1 criteria was used for assessment.

DEMERITS OF THIS STUDY:

- There wasn't long term follow up of this study, so progression free survival, overall survival could not be assessed.
- Radiation delivery was given through 2D technique.
- This is a single arm phase two trial, hence double armed study and randomized control trial must follow to determine prognostic significance and survival rates.

Future perspective:

This study further established the feasibility and efficacy of concurrent Capecitabine and weekly Cisplatin with radiation in locally advanced head and neck cancers. Randomized trial using the same protocol is recommended.

CONCLUSION

CONCLUSION

The head and neck cancer burden is a distressing problem in the developing countries like India. Inspite of the effective ban on the tobacco usage, the consumers of tobacco and alcohol is rising. Also most of our people are in low socioeconomic status, illiterate and lack of awareness of medical attention; makes people to present in locally advanced stage. Hence locoregional control becomes a challenge. Many concurrent chemoradiation trials are upcoming in head and neck squamous cell carcinoma.

The aim of this study was to evaluate and explore Capecitabine and weekly cisplatin concurrently with conventional radiation. The dose of weekly cisplatin 40mg/m^2 and Capecitabine 500mg/m^2 twice bid has shown effective locoregional control with a complete response of 73% and partial response was 27% with manageable toxicity.

Though there is lack of long term follow up of this study, locoregional control was effective. Large scale randomized study are recommended in near future for PFS and OS.

This study of concurrent chemoradiation with Capecitabine and weekly cisplatin is a feasible option in our patients with manageable toxicity.

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APPENDIX 1

TABLE NUMBER	TITLE
1	Cancer trend
2	Head and neck cancer Site (1)
3	Head and neck cancer site (2)
4	Age distribution of study population
5	Gender distribution of study population
6	ECOG performance status
7	Habits/ addiction of the study population
8	Symptoms / Signs
9	Primary site
10	Subsite analysis
11	Tumor Tstage
12	Nodal N Stage
13	Stage grouping
14	Histological differentiation
15	Response results
16	Site Vs response
17	T stage Vs response
18	N nodal stage Vs Response
19	Histological response Vs Response
20	ECOG Vs Response
21	Age Vs response
22	Stage Vs response
23	Treatment Vs response
24	Acute Toxicity
25	Systemic toxicity
26	Anemia
27	Cisplatin Response
28	Capecitabine trials

APPENDIX 2

FIGURE	TITLE
1	HPV biological action
2	Lymph nodes levels
3	Age distribution of the study population
4	Gender distribution of the study population
5	ECOG performance status
6	Symptoms and signs
7	Site distribution of the study population
8	Subsite Analysis
9	T stage in the study population
10	Nodal stage in the study population
11	Stage grouping
12	Treatment results - Response
13	Site Vs Response
14	T stage Vs Response
15	Nodal stage vs Response
16	Histologic differentiation Vs Response
17	Response in the Primary
18	Response in the Nodes
19	Treatment delay
20	Response Vs Treatment break
21	Acute toxicity
22	Systemic Toxicity
23	Hematological Toxicity

APPENDIX 3

RTOG ACUTE RADIATION MORBIDITY CRITERIA

SITE	GRADE 0	GRADE1	GRADE2	GRADE3	GRADE 4
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous Membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste		Acute salivary gland necrosis

Pharynx & Esophagus	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyper alimentation	Complete obstruction, ulceration, perforation, fistula
Laryngitis	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

HEMATOLOGIC TOXICITY

Grade	0	1	2	3	4
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-

APPENDIX 4

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

CTCAE VERSION 4

GRADE	1	2	3	4
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated	-
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	>/=6 episodes (separated by 5 minutes) in 24 hrs,tubefeeding,TPN or hospitalization indicated	Life-threatening consequences, urgent intervention indicated
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per da over baseline; moderate increase in ostomy output compared to baseline	Increase of =7 stools per day over baseline; incontinence; hospitalization indicated;severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

ANNEXURES

ANNEXURES I

INFORMATION TO PARTICIPANTS

Title: - "**CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN**"

Principal Investigator:
Co-Investigator: Dr. Ramya.A.
Name of Participant:
Site :Department of radiotherapy

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Head and neck cancer is widely prevalent in India, and about 16% cancer related deaths are due to head and neck cancer. Majority of the patients present with a locoregionally advanced disease where the management becomes quite challenging. The oral fluoropyrimidinecapecitabine was rationally designed to preferentially generate 5 -FU in tumour tissue and mimic continuous-infusion 5 -FU. This selectivity is achieved through exploiting the significantly higher activity of thymidine phosphorylase (TP) in many tumour tissues compared with healthy tissue.

Concurrent chemoradiotherapy - Radiotherapy will be delivered by opposing lateral fields with a telecobalt machine in 200cGy per fraction for 5 days a week. Patients are given a break on Saturday and Sunday. Weekly Cisplatin chemotherapy is given every Monday before radiation and Tab. Capecitabine daily. Entire treatment is to be completed in less than 7 weeks time. Primary and gross adenopathy receive 66 Gy
We have obtained permission from the Institutional Ethics Committee.

The study design
Single arm prospective study

Study Procedures

The study involves evaluation of Locally advanced squamous cell carcinoma of the head and neck with radiotherapy and chemo in the form weekly inj.cisplatin and daily tab.capecitabine. Every week before chemotherapy, the study physician will examine you. Some [blood / urine /clinical examination other] tests will be carried out at each visit. [… … ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.] These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.
In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.

You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator — Signature of Participant

Date — Date

ANNEXURES II

INFORMED CONSENT FORM

TITLE OF THE STUDY **:**"CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : DR.A.RAMYA,
NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****
8. I have not participated in any research study within the past 12 month(s). *****
9. I agree to undergo complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

ANNEXURES III

ஆராய்ச்சிதகவல் தாள்

ஆராய்ச்சியின் பெயர்:

*தலைமற்றும்கழுத்துபகுதியில்உள்ளமுற்றியச்கோமஸ்செல்வகைபுற்றுநோய்க்குகதிர்வீச்சுசிகிச்சையும்*கேப்பசிட்டாபின் மாத்திரை*மற்றும் வாரம்ஒருமுறைபுற்றுநோய்மருந்து*சிஸ்பிளாட்டின் *கொடுத்துபுற்றுநோயைகுணப்படுதுவது*

ஆராய்ச்சியாளர் பெயர்:

பங்கேற்பாளர் பெயர்:

சென்னை இராஜீவ்காந்திஅரசுபொதுமருத்துவமனைக்குவரும் தலைமற்றும் கழுத்துபகுதிபுற்றுநோய் நோயாளியிகளிடம் கதிர்வீச்சுசிகிச்சைபற்றியஆராய்ச்சி.

தலைமற்றும் கழுத்துபகுதியில் முற்றிய புற்றுநோய்க்கு பலவகையான கதிர்வீச்சுசிகிச்சை முறைகள் உள்ளன.

*"தலைமற்றும்கழுத்துபகுதியில்உள்ளமுற்றியச்கோமெளஸ்செல்வகைபுற்று நோய்க்குகதிர்வீச்சுசிகிச்சையும்*கேப்பசிட்டாபின்மாத்திரை *மற்றும்வாரம்ஒருமுறைபுற்றுநோய்மருந்து*சிஸ்பிளாட்டினம்*கொடுத்துபுற்றுநோயைகுணப்படுதுவது*" பற்றிஆராய்வது இந்தஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் கதிர்வீச்சுசிகிச்சை மற்றும் புற்றுநோய் மருந்து அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடுமபோதோ அல்லது ஆராய்ச்சியின்போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மைபற்றியும் ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

_____ _____

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

ANNEXURES IV

ஆராய்ச்சிஒப்புதல் கடிதம்

பெயர்: *தேதி:*

வயது: *உள்/புற நோயாளி எண்:*

பால்: *ஆராய்ச்சி சேர்க்கை எண்:*

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்றுநோய் நோயாளியிகளிடம் கதிர்வீச்சு சிகிச்சை பற்றிய ஆராய்ச்சி.

துலை மற்றும் கழுத்துபகுதியில் முற்றிய புற்றுநோய்க்கு பலவகையான கதிர்வீச்சுசிகிச்சைமுறைகள்

உள்ளன.*"தலைமற்றும்கழுத்துபகுதியில்உள்ளமுற்றியச்கோமெளஸ்செல்வ கைபுற்றுநோய்க்குகதிர்வீச்சுசிகிச்சையும்*கேப்பசிட்டாபின்மாத்திரை *மற்றும் வாரம்ஒருமுறைபுற்றுநோய்மருந்துசிஸ்பிளாட்டினம்கொடுத்துபுற்றுநோயைகு ணப்டுதுவது"*இந்தஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் கதிர்வீச்சுசிகிச்சை மற்றும் புற்றுநோய் மருந்து அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடுமபோதோ அல்லது ஆராய்ச்சியின்போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மைபற்றியும் ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

_____ _____

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

ANNEXURES V

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. A. Ramya,
PG in Radio Therapy,
Department of Radio Therapy,
Madras Medical College, Chennai-3.

Dear Dr. A. Ramya,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Concurrent Chemoradiotherapy In Locally Advanced Squamous Cell Carcinoma Of Head And Neck With Capecitabine And Weekly Cisplatin"** No.03032014

The following members of Ethics Committee were present in the meeting held on 11.03.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Prof. Kalaiselvi, MD Vice-Principal, MMC, Ch-3	-- Member Secretary
3.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
4.	Prof. Bhavani Shankar, M.S. Prof & HOD of General Surgery, MMC, Ch-3.	-- Member
5.	Prof. V. Padmavathi, M.D. I/c Director of Pathology, MMC, Ch-3.	-- Member
6.	Thiru. S. Govindasamy, BABL	-- Lawyer
7.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

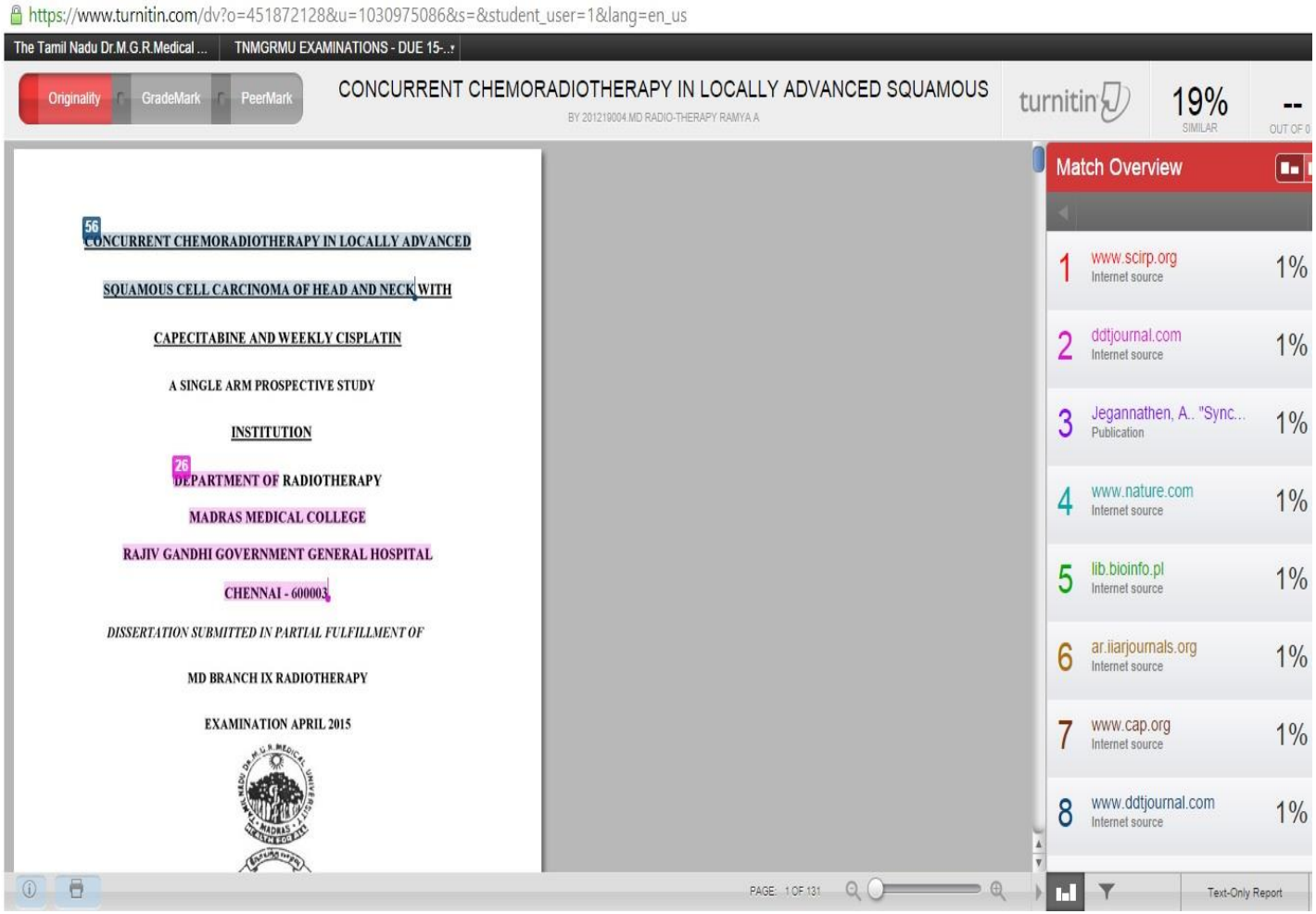
13/3/14

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

13/3/14

ANNEXURE VI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A SINGLE ARM PROSPECTIVE STUDY
INSTITUTION
26
DEPARTMENT OF RADIOTHERAPY
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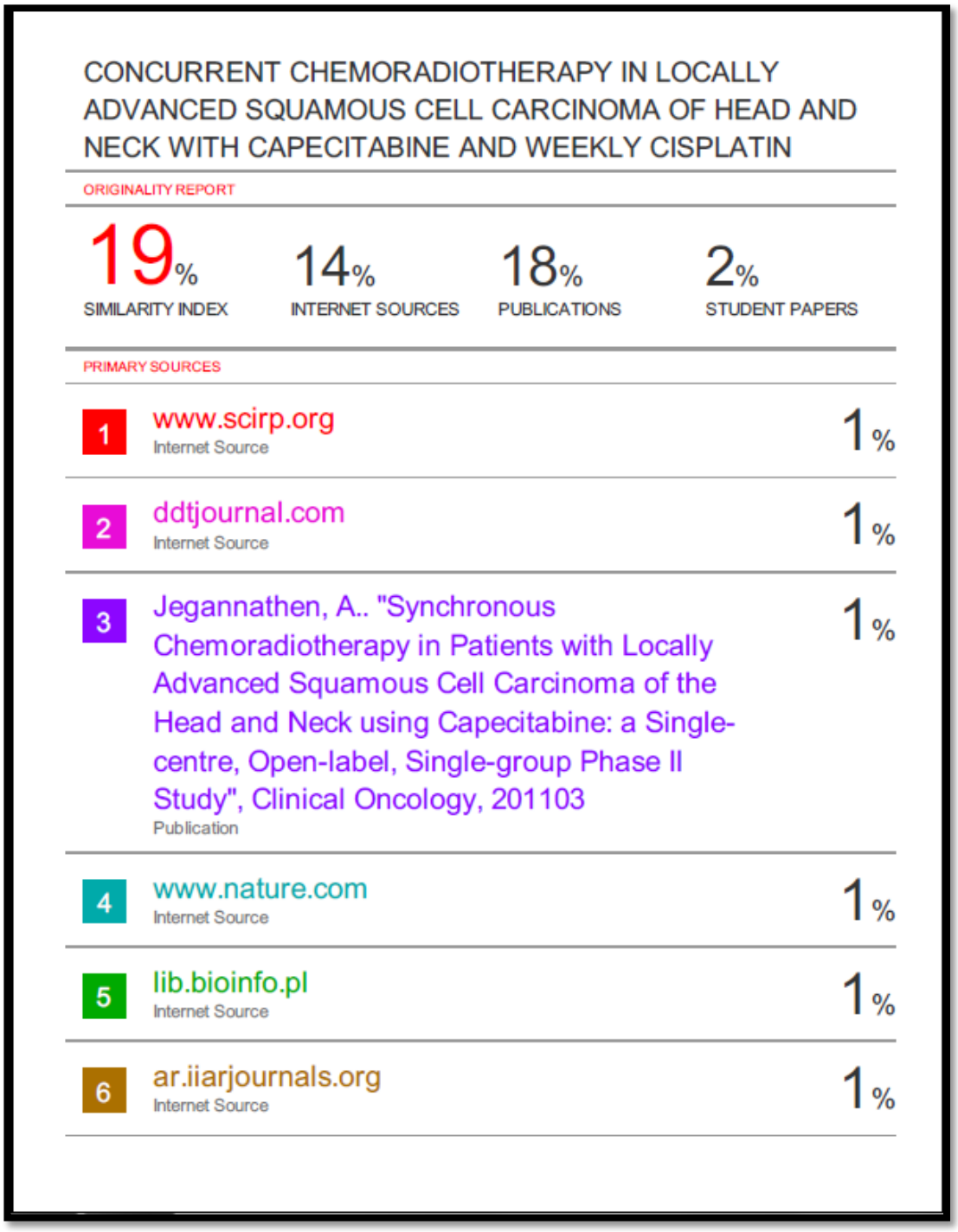
ANNEXURE VII



CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CAPECITABINE AND WEEKLY CISPLATIN

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3	Jegannathen, A.. "Synchronous Chemoradiotherapy in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck using Capecitabine: a Single-centre, Open-label, Single-group Phase II Study", Clinical Oncology, 201103 Publication	1%
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